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

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Locally advanced or metastatic squamous cell head and neck cancer in patients where CISplatin is contraindicated or not tolerated.	C76	00418a	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.

Cetuximab is administered once weekly on days 1, 8 and 15, CARBOplatin is administered on Day 1 and 5-Fluorouracil is administered on days 1-4 of a 21 day cycle for up to 6 cycles until disease progression or unacceptable toxicity develops.
Systemic anti-cancer therapy (SACT) must not be administered earlier than 1 hour after the end of the cetuximab infusion.

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

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 2 hours	1
	8,15	Cetuximab	250mg/m^2	[a]IV Observe post infusion	Over 60 minutes	1
1	1,8,15	Cetuximab	250mg/m^2	IV	Over 60 minutes	2 onwards
2	1	CARBOplatin	AUC 5	IV infusion	500mL glucose 5% over 30 minutes	1-6
3	1-4	[c,d]5-Fluorouracil	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/minute. 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/minute. 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-Fluorouracil 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
[d]See dose modifications section for patients with identified partial Dihydropyrimidine dehydrogenase (DPD) deficiency.

CARBOplatin dose:

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

Dose (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 may be performed using the Wright formula to estimate GFR or the Cockcroft and Gault formula to estimate creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- For obese patients and those with a low serum creatinine, for example, due to low body weight or post-operative asthenia, estimation using formulae may not give accurate results; measured GFR is recommended.
    - where obesity (body mass index [BMI] ≥ 30 kg/m^2) or overweight (BMI 25-29.9) is likely to lead to an overestimate of GFR and isotope GFR is not available the use of the adjusted ideal body weight in the Cockcroft and Gault formula may be considered.
    - where serum creatinine is less than 63 micromol/L, the use of a creatinine value of 62 micromol/L or a steady pre-operative creatinine value may be considered
- These comments do not substitute for the clinical judgement of a physician experienced in prescription of CARBOplatin.

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

GFR (mL/min) = S x (140 - age in years) x wt (kg)
serum creatinine (micromol/L)

S= 1.04 for females and 1.23 for males

ELIGIBILITY:

- Indication 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 xULN, bilirubin ≤ 1.5 x ULN

EXCLUSIONS:

- Hypersensitivity to cetuximab, CARBOplatin*, 5-Fluorouracil or any of the excipients
- Lactation
- Known complete 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 hepatic profile (including magnesium)
- ECG (if patient has compromised cardiac function).
- Isotope GFR measurement (preferred) or GFR / Cr Clearance estimation
- 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.
- 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 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:

- 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 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. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2. 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 Cockcroft & Gault or Wright formula are used, the dose should be calculated as required on each 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 Cockcroft & Gault or Wright formulae.

Non-haematological toxicity:

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

Adverse reaction	Discontinue	Recommended dose modification
Infusion Reaction Grade 1 Grade 2 Grade 3 and 4		 Continue slow infusion under close supervision. Continue slow infusion and immediately administer treatment for symptoms. Stop infusion immediately, treat symptoms vigorously and contraindicate further use of cetuximab
Interstitial lung disease	Discontinue	
Skin reaction 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 ≥ grade 3*		
First occurrence		Hold cetuximab treatment for a maximum of 2 weeks. Reinitiate therapy only if reaction has resolved to grade 2 at **250mg/m²**
Second occurrence		Hold cetuximab treatment for a maximum of 2 weeks. Reinitiate therapy only if reaction has resolved to grade 2 at **200mg/m²**
Third occurrence		Hold cetuximab treatment for a maximum of 2 weeks. Reinitiate therapy only if reaction has resolved to grade 2 at **150mg/m²**
Fourth occurrence	Discontinue	

*** 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 at least one hour 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 as to 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:** 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 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 dihydropyrimidine dehydrogenase (DPD).
- Current drug interaction databases should be consulted for more information.

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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
4	26/08/2020	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
5	28/04/2021	Reviewed. Updated Cetuximab premedication timing.	Prof Maccon Keane

6	29/09/2023	Updated CARBOplatin infusion time. Updated standard wording for CARBOplatin dosing , renal dysfunction and creatinine value. Updated baseline tests and exclusions section.	Prof Maccon Keane
6a	03/03/2025	Additional wording added to baseline testing section.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.