Cetuximab (weekly), CISplatin 100mg/m^2 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 carcinoma of the head and neck	C76	00417a	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.

Cetuximab is administered once weekly on days 1, 8 and 15, CISplatin 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.

Chemotherapy must not be administered earlier than 1 hour after the end of the cetuximab infusion.

Maintenance cetuximab may be considered following the end of this treatment as per regimen 00207 Cetuximab Monotherapy-7 days

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 120mins	1
	8,15	Cetuximab	250mg/m^2	[a]IV Observe post infusion	Over 60mins	1
	1,8,15	Cetuximab	250mg/m^2	IV	Over 60mins	2 onwards
2	1	[c]CISplatin	100mg/m^2	IV infusion	1000ml 0.9% NaCl over 2 hours	1-6
3	1-4	[d,e]5-Fluorouracil	1000mg/m^2/day	Continuous IV infusion	1000ml 0.9% NaCl over 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]**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 10-20mmol/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 (2, 3).
[d]Alternatively 5-Fluorouracil may be administered at 2000mg/m^2 over 46-48 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
[e]See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency

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 x ULN, bilirubin ≤1.5 x ULN

EXCLUSIONS:

- Hypersensitivity to cetuximab, CISplatin, 5-Fluorouracil or any of the excipients
- Lactation
- Pre existing neuropathies ≥ grade 2
- Moderate/severe renal impairment (creatinine clearance < 60 mL/min)
- Significant hearing impairment/tinnitus
- 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 hepatic profile (including magnesium)
- ECG (if patient has compromised cardiac function)
- Audiology and creatinine clearance 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

Regular tests:

- FBC
- Renal and hepatic profile before each cycle (including magnesium)
- 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 haematological 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 CISplatin and 5-Fluorouracil by 25% for subsequent cycles
Febrile neutropenia			

Renal and Hepatic Impairment:

Table 2: Dose modification for renal and hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal Impairment</th><th colspan="4">Hepatic Impairment</th></tr>
<tr><td>Cetuximab</td><td colspan="2">Clinical decision-unlikely to require a reduction.</td><td colspan="4">Unlikely to require a dose reduction.</td></tr>
<tr><td rowspan="4">CISplatin</td><td>CrCl (ml/min)</td><td>Dose</td><td colspan="4" rowspan="4">No dose reduction necessary.</td></tr>
<tr><td>≥60</td><td>100%</td></tr>
<tr><td>45-59</td><td>75%</td></tr>
<tr><td><45</td><td>Clinical decision.
Consider using carboplatin.</td></tr>
<tr><td rowspan="4">5-Fluorouracil</td><td colspan="2" rowspan="4">Consider dose reduction in severe renal impairment only.</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.
Moderate hepatic impairment; reduce initial dose by 1/3.
Severe hepatic impairment, reduce initial dose by 1/2.
Increase dose if no toxicity.</td></tr>
</table>

Non-haematological toxicity

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

Drug	Adverse reaction	Discontinue	Recommended dose modification
Cetuximab	Infusion Reaction Grade 1		Continue slow infusion under close supervision.
	Grade 2		Continue slow infusion and immediately administer treatment for symptoms.
	Grade 3 and 4		Stop infusion immediately, treat symptoms vigorously and contraindicate further use of cetuximab
Cetuximab	Interstitial lung disease	Discontinue	
Cetuximab	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	
CISplatin	Grade ≥ 2 peripheral neuropathy		Omit CISplatin and consider substituting CISplatin with carboplatin

* See other supportive care section below

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- **Cetuximab** Low (**Refer to local policy**)
- **CISplatin** High (**Refer to local policy**)
- **5-Fluorouracil** Low (**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
- Hydration prior and post CISplatin administration (**Refer to local policy** or see recommendations above)

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.

CISplatin

- **Renal toxicity:** Renal toxicity is common with CISplatin. Encourage oral hydration.
- **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle.

5-Fluorouracil

- **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:

- Avoid concurrent use of CISplatin with nephrotoxic or ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive toxicity. If necessary, monitor renal function closely.
- 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.
- 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	9/01/2019	Standardisation of treatment table. Updated with revised CISplatin hydration regimen recommendations,	Prof Maccon Keane
3	16/05/2019	Update of exclusion criteria, emetogenic potential, tests, and drug interactions, hepatic dose modifications	Prof Maccon Keane
4	09/10/2019	Update of exclusion criteria	Prof Maccon Keane
5	26/8/2020	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
6	28/04/2021	Reviewed. Amended Cisplatin prehydration in treatment table (KCl) and updated Cetuximab premedication timing.	Prof Maccon Keane
6a	21/11/2023	Formatting changes and grammatical corrections.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.