Cetuximab Therapy-7 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
As monotherapy for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing RAS wild-type metastatic colorectal cancer (mCRC) in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan	C18	00207a	Hospital
Treatment of patients with squamous cell cancer of the head and neck: In combination with radiation therapy for locally advanced disease.	C76	00207b	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 a week. The initial dose is 400 mg/m^2.
All subsequent weekly doses are 250 mg cetuximab/m^2

Colorectal cancer: Treatment continued until disease progression or unacceptable toxicity.

Locally advanced squamous cell cancer of the head and neck: Used concomitantly with radiation therapy. It is recommended to start cetuximab therapy one week before radiation therapy and to continue cetuximab therapy until the end of the radiation therapy period.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Cetuximab	400mg/m^2	IV Infusion. Observe post infusion*	Over 2 hrs**	1
1	Cetuximab	250mg/m^2	IV Infusion. Observe post infusion*	Over 60mins	2 and further cycles

*Obtain vital signs pre-infusion, at 1 hr and post-infusion. 1hr observation period following end of 1st and 2nd cetuximab infusions.
If no infusion reactions occur for 2 consecutive doses, then may discontinue observation period and vital signs.

**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.

ELIGIBILTY:

- Indications as above
  - Wild type RAS tumours verified by a validated test method
  - ECOG 0-3
  - Adequate marrow reserve
  - Adequate renal and liver function

EXCLUSIONS:

- Hypersensitivity to the cetuximab or to any of the excipients.
- Patients with mutant RAS mCRC or unknown RAS mCRC status

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- 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 liver profile
- 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.

Renal and Hepatic Impairment:

Table 1: Dose modification of cetuximab in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
Clinical decision – unlikely to require a reduction.	Unlikely to require a reduction.

Management of adverse events:

Table 2: Dose Modification of cetuximab for Adverse Events

Adverse reactions	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 treatment
Skin reaction grade 1 or 2 Severe skin reaction ≥ grade 3* First occurrence Second occurrence Third occurrence Fourth occurrence	No dosage adjustment required. See local skin care policy for the prevention and treatment of EGFR-inhibitor adverse skin reactions. Hold cetuximab treatment for a maximum of 2 weeks. Reinitiate therapy only if reaction has resolved to grade 2 at **250**mg/m^2 Hold cetuximab treatment for a maximum of 2 weeks. Reinitiate therapy only if reaction has resolved to grade 2 at **200**mg/m^2 Hold cetuximab treatment for a maximum of 2 weeks. Reinitiate therapy only if reaction has resolved to grade 2 at **150**mg/m^2 Discontinue

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low (**Refer to local policy).**

PREMEDICATIONS:

Patients must receive premedication with:

- antihistamine
- corticosteroid.

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

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

- **Infusion-related reactions (IRR):**
  - 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 2)
  - 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 EGRF 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 2 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.

DRUG INTERACTIONS:

- May result in increased frequency of severe leukopenia or severe neutropenia when used in combination with platinum based chemotherapy
- In combination with fluoropyrimidines, the frequency of palmar-plantar erythrodysaesthesia and of cardiac ischaemia including myocardial infarction and congestive heart failure were increased
- In combination with capecitabine and oxaliplatin the frequency of severe diarrhoea may be increased.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Cetuximab L01XC06

REFERENCES:

1. Cunningham D, et al: Cetuximab Monotherapy and Cetuximab plus Irinotecan in Irinotecan-Refractory Metastatic Colorectal Cancer. NEJM 2004; 351:337 – 345.
2. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous cell carcinoma of the head and neck. N Engl J Med 2006;354:567-78.
3. Vermorken JB, Ricard MD, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-27.
4. Irish Medicines Board :Drug Safety Newsletter April 2014 – Issue Number 60 Available at https://www.hpra.ie/docs/default-source/publications-forms/newsletters/drug-safety-newsletter-issue-no-60-april-2014.pdf?sfvrsn=12
5. Cetuximab (Erbitux®) Summary of Product Characteristics. Last upated: 04/09/2019. Accessed January 2020. Available at https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	10/02/2014		Dr Maccon Keane
2	10/02/2016	Expanded information on management of infusion reactions. Clarified infusion rate of first infusion	Prof Maccon Keane
3	07/02/2018	Clarified indications and updated with new NCCP regimen template	Prof Maccon Keane
4	12/02/2020	Regimen review. Standardisation of renal and hepatic impairment	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.