PACLitaxel (Day 1, 8 and 15) and Cetuximab (Day 1 and 15) Therapy – 28 day[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
For the treatment of patients with recurrent and / or metastatic squamous cell carcinoma of the head and neck[ii]	C76	00696a	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.

PACLitaxel is administered on Days 1, 8 and 15 and cetuximab is administered on Days 1 and 15.

Each cycle is 28 days.

Treatment with both drugs is administered until disease progression or unacceptable toxicity.

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

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	**1, 15**	Cetuximab	500mg/m^2	IV infusion Observe post infusion[a]	See footnote[b] below	Every 28 days
2	**1, 8, 15**	PACLitaxel[c, d]	80mg/m^{2e}	IV infusion	250 mL NaCl 0.9% over 1 hour	Every 28 days
[a] Obtain vital signs pre-infusion, at 1 hour and post-infusion. 1 hour 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.						
[b] The initial dose should be given slowly and speed of infusion must not exceed 5 mg/minute. For subsequent doses, the maximum infusion rate must not exceed 10 mg/minute if no adverse reaction to first infusion. May be administered diluted in NaCl 0.9% or undiluted. Flush the line with NaCl 0.9% at the end of the cetuximab infusion.						
[c] PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an inline 0.22 µm filter with a microporous membrane.						
[d] PACLitaxel should be diluted to a concentration of 0.3-1.2mg/mL.						
[e] Some patients may be initiated at a dose of 100mg/m^2 (in line with Koyama T et al, 2024) at the discretion of the prescribing clinician.						

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

- Indication as above
- ECOG 0-2
- Adequate organ function

EXCLUSIONS:

- Hypersensitivity to cetuximab, PACLitaxel or any of the excipients
- Pregnancy
- Breastfeeding
- Baseline neutrophil count < $1.5x10^9$ cells/L
- Severe hepatic impairment

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
- Assessment of peripheral neuropathy status as clinically indicated

Regular tests:

- FBC, renal and liver profile
- Assessment of peripheral neuropathy status as clinically indicated

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: Recommended dose reduction schedule for PACLitaxel

Dose Reduction Schedule	Dose Level*
Starting dose	80mg/m^2
First dose reduction	65mg/m^2
Second dose reduction	50mg/m^2
*To note, for patients who are initiated at a dose of 100mg/m^2, the first reduced dose level should be 80mg/m^2.	

Table 2: Recommended dose modifications for PACLitaxel for haematological toxicity

ANC (x10^9/L)		Platelets	Dose
≥1.0	and	≥90	100%
0.5 – 0.99	and/or	70-90	Delay and consider dose reduction at subsequent cycle
<0.5 for ≥7days	and/or	<70	Delay and reduce by one dose level after recovery. Consider addition of GCSF.
Febrile neutropenia			

Renal and Hepatic Impairment:

Table 3: Dose modification of cetuximab and PACLitaxel in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment			
Cetuximab[a]	Renal impairment: No need for dose adjustment is expected Haemodialysis: No need for dose adjustment is expected	Hepatic impairment: No need for dose adjustment is expected			
PACLitaxel[b]	Renal impairment: No need for dose adjustment is expected Haemodialysis: No need for dose adjustment is expected	**ALT**		**Total Bilirubin**	**Dose**
		< 10 x ULN	and	≤ 1.25 x ULN	80mg/m^2
		< 10 x ULN	and	1.26-2 x ULN	60mg/m^2
		< 10 x ULN	and	2.01-5 x ULN	40mg/m^2
		≥ 10 x ULN	or	> 5 x ULN	Contraindicated

[a] Cetuximab: Renal and hepatic – Giraud et al 2023
[b] PACLitaxel: Renal and hepatic – Giraud et al 2023

Management of adverse events:

Table 4: Recommended dose modification of PACLitaxel for Adverse Events

Adverse reactions	Dose
Grade 2 motor or sensory neuropathy	Decrease dose by 10mg/m^2
All other grade 2 non-haematological toxicity	Hold treatment until toxicity resolves to ≤ grade 1. Decrease subsequent doses by 10mg/m$^{2.}$
≥ Grade 3 reaction	Consider reduction by one dose level after recovery

Table 5: Dose modification schedule for cetuximab based on Adverse Events

Adverse reaction	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** **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 **500**mg/m^2 Hold cetuximab treatment for a maximum of 2 weeks. Reinitiate therapy only if reaction has resolved to grade 2 at **400**mg/m^2 Hold cetuximab treatment for a maximum of 2 weeks. Reinitiate therapy only if reaction has resolved to grade 2 at **300**mg/m^2 Discontinue

* See other supportive care section below

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting- Available on NCCP website

Cetuximab: Low **(Refer to local policy)**
PACLitaxel: Low **(Refer to local policy)**

For information:

Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on NCCP website

PREMEDICATIONS:

Cetuximab:

- Patients must receive premedication with an antihistamine and a corticosteroid before receiving cetuximab infusion (as detailed in Table 6 below). This premedication is recommended prior to all subsequent infusions. Patients should be educated about the possibility of delayed infusion-related symptoms.

Table 6: Suggested pre-medications prior to cetuximab infusion

Drugs	Dose	Route
Chlorphenamine	10mg	IV bolus 60 minutes prior to cetuximab infusion
dexAMETHasone	8mg	IV bolus 60 minutes prior to cetuximab infusion

To note:

On treatment days where both cetuximab and PACLitaxel are administered, the premedication (corticosteroid and antihistamine) for PACLitaxel will be covered by the cetuximab premedication, with H_2 antagonist as set out in Table 7: Suggested premedications prior to treatment with PACLitaxel.

PACLitaxel:

- All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to first dose of PACLitaxel treatment.
- The H_2 antagonist, famotidine, can potentially be omitted from the pre-medication requirements for PACLitaxel but the risk of hypersensitivity with this approach is unknown.
  - Where a patient experiences hypersensitivity, consider the use of alternative H_2 antagonists **(Refer to local policy).**

Table 7 outlines suggested premedications prior to treatment with PACLitaxel.

Table 7: Suggested premedications prior to treatment with PACLitaxel

Day of treatment	Drug	Dose	Administration prior to PACLitaxel
Day 1	dexAMETHasone[a]	8mg IV	30 minutes
Day 1	Chlorphenamine	10mg IV	30 minutes
Day 1	Famotidine	20mg IV	30 minutes
Day 8[b] and thereafter	dexAMETHasone[a]	None	
Day 8 and thereafter	Chlorphenamine	10mg IV	30 minutes
Day 8 and thereafter	Famotidine[c]	20mg IV	30 minutes
[a]Dose of dexAMETHasone may be altered, in the event of hypersensitivity reaction, to 20 mg of dexAMETHasone orally 12 hour and 6 hour prior to re-challenge with PACLitaxel according to consultant guidance.			
[b]Dose of dexAMETHasone may be added from day 8 if increased risk or previous hypersensitivity reaction according to consultant guidance.			
[c]Dose of famotidine may be omitted in the absence of hypersensitivity reaction according to consultant guidance.			

OTHER SUPPORTIVE CARE:

- See local skin care policy for the prevention and treatment of EGFR-inhibitor adverse skin reactions **(Refer to local policy).**
- Myalgias and arthralgias may occur with PACLitaxel. Analgesic cover should be considered.

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

1. Koyama T et al. A phase II trial of paclitaxel plus biweekly cetuximab for patients with recurrent or metastatic head and neck cancer previously treated with both platinum-based chemotherapy and anti-PD-1 antibody. ESMO Open. 2024 Jun;9(6):103476. doi: 10.1016/j.esmoop.2024.103476. Epub 2024 Jun 3. Erratum in: ESMO Open. 2024 Aug;9(8):103652. doi: 10.1016/j.esmoop.2024.103652. PMID: 38833968; PMCID: PMC11179070.
2. Hitt R et al. Spanish Head and Neck Cancer Cooperative Group (TTCC). Phase II study of the combination of cetuximab and weekly paclitaxel in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. Ann Oncol. 2012 Apr; 23(4):1016-22. doi: 10.1093/annonc/mdr367. Epub 2011 Aug 23. PMID: 21865152.
3. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
4. 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
5. Cetuximab (Erbutix®) Summary of Product Characteristics. Last updated 05/06/2024. Accessed 04/07/2024. Available at: https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf
6. PACLitaxel 6mg/mL Summary of Product Characteristics. Last updated 21/09/2022. Accessed 04/07/2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-050-001_21092022103217.pdf

Version	Date	Amendment	Approved By
1	07/02/2025		Dr Colm Mac Eochagain

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed posology for the use of cetuximab and PACLitaxel in Ireland. Patients should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.

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