DOCEtaxel (75), CISplatin (75), 5-Fluorouracil (1000), Chemoradiation and Surgery - Neoadjuvant (TCF)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Induction treatment of patients with Stage III or IV non-metastatic squamous cell carcinoma of the head and neck.	C76	00315a	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 patient's individual clinical circumstances.

Induction Chemotherapy	DOCEtaxel and CISplatin are administered on day 1 and 5-Fluorouracil is administered on days 1-4 of a **21** day cycle for 3 cycles unless disease progression or unacceptable toxicity develops (Ref Treatment Table 1).
Chemoradiation In patients who do not have progressive disease and with adequate bone marrow function	CARBOplatin AUC 1.5 weekly concomitantly with radiotherapy for 7 weeks to start 3 to 8 weeks (day 22 to day 56) following start of third cycle of induction chemotherapy (Reference NCCP Regimen 00322 CARBOplatin (AUC1.5) Chemoradiation Therapy-7 days).
Surgery	Considered 6-12 weeks following completion of chemoradiation.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered on Day 1.

Table 1: Treatment Table for Induction Chemotherapy with DOCEtaxel, CISplatin and 5-Fluorouracil

Admin. Order	Day	Drug	Dose	Route and Method of Administration	Diluent & Rate	Cycle
1	1	DOCEtaxel	75mg/m^2	IV infusion	[a]250mL 0.9% NaCl over 60 minutes	Every 21 days for 3 cycles
2	1	[b]CISplatin	75mg/m^2	IV infusion	1000mL 0.9% NaCl over 2 hours	Every 21 days for 3 cycles
3	1-4	[c]5-Fluorouracil	1000mg/m^2	IV infusion	1000mL 0.9% NaCl over 22 hours	Every 21 days for 3 cycles

[a]75-185mg dose use 250mL infusion bag. For doses> 185mg use 500mL infusion bag
Use non-PVC infusion bag.

[b] **Pre and post hydration therapy required for CISplatin**
See local hospital policy recommendations.
Suggested pre hydration for CISplatin therapy:
1. Administer 10mmol magnesium sulphate ($MgSO_4$) (+/-KCl 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 (4, 5).

[c] See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency

ELIGIBILITY:

- Indications as above
- Life expectancy > 3months
- ECOG status 0-1
- Adequate organ function; ANC > 1.5 x10^9 cells/L, platelets 100 x10^9/L
- Planned for definitive chemoradiation and surgery

EXCLUSIONS:

- Hypersensitivity to DOCEtaxel, CISplatin, 5-Fluorouracil or any of the excipients
- Pregnancy
- Lactation
- Pre-existing neuropathies ≥ grade 2
- Severe liver impairment
- 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 liver profile
- ECG (if patient has compromised cardiac function)
- Audiology and creatinine clearance if clinically indicated
- 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 liver profile* before each cycle
  *See Adverse Effects/Regimen specific complications for guidelines regarding hepatic dysfunction with DOCEtaxel

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 2: Dose modification for haematological toxicity

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose of DOCEtaxel
≥1.5	and	≥100	100%
<1.5	or	<100	Delay until recovery
		<25	Delay until recovery and reduce DOCEtaxel dose to 60mg/m^2

- If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the DOCEtaxel dose should be reduced from 75 to 60 mg/m^2.
- If subsequent episodes of complicated neutropenia occur the DOCEtaxel dose should be reduced from 60 to 45 mg/m^2.
- In the pivotal SCCHN studies patients who experienced complicated neutropenia (including prolonged neutropenia, febrile neutropenia, or infection), it was recommended to use G-CSF to provide prophylactic coverage (e.g. day 6-15) in all subsequent cycles.

Renal and Hepatic Impairment:

Table 3: Dose modification for renal and hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal Impairment</th><th colspan="6">Hepatic Impairment</th></tr>
<tr><td rowspan="3">DOCEtaxel</td><td colspan="2" rowspan="3">No data available in patients with severely impaired renal function</td><td>Serum Bilirubin</td><td></td><td>AST and/or ALT</td><td></td><td>ALP</td><td>Dose</td></tr>
<tr><td></td><td></td><td>> 1.5 ULN</td><td>and</td><td>> 2.5 ULN</td><td>75 mg/m^2</td></tr>
<tr><td>>ULN</td><td>and /or</td><td>> 3.5 ULN (AST and ALT)</td><td>and</td><td>> 6 ULN</td><td>Stop treatment unless strictly indicated and should be discussed with a Consultant.</td></tr>
<tr><td rowspan="4">CISplatin</td><td>CrCL (ml/min)</td><td>Dose</td><td colspan="6" 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</td><td></td><td>AST</td><td colspan="3">Dose</td></tr>
<tr><td><85</td><td></td><td><180</td><td colspan="3">100%</td></tr>
<tr><td>>85</td><td>or</td><td>>180</td><td colspan="3">Contra-indicated</td></tr>
<tr><td colspan="6">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>

ALP = Alkaline Phosphatase, ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase ULN = Upper Limit of Normal

Non-haematological toxicity:

Table 4: Dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
Grade 3 diarrhoea • 1st episode • 2nd episode	• Reduce 5-Fluorouracil dose by 20% • Reduce DOCEtaxel dose by 20%
Grade 4 diarrhoea • 1st episode • 2nd episode	• Reduce DOCEtaxel and 5-Fluorouracil dose by 20% • Discontinue treatment
Grade 3 stomatitis/mucositis • 1st episode • 2nd episode • 3rd episode	• Reduce 5-Fluorouracil dose by 20% • Stop 5-Fluorouracil only, at all subsequent cycles • Reduce DOCEtaxel dose by 20%
Grade 4 stomatitis/mucositis • 1st episode • 2nd episode	• Stop 5-Fluorouracil only, at all subsequent cycles • Reduce DOCEtaxel dose by 20%.
Grade 3 skin reaction	Decrease dose of DOCEtaxel to 60mg/m^2 If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued
Grade >2 peripheral neuropathy	Decrease dose of DOCEtaxel to 60mg/m^2 If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued Consider dose reduction of CISplatin at discretion of prescribing consultant
Grade ≥ 2 PPE	Delay 5-Fluorouracil until recovery to Grade ≤ 1 and reduce subsequent doses of 5-Fluorouracil by 20%

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

DOCEtaxel: Low **(Refer to local policy)**

CISplatin: High **(Refer to local policy)**

5-Fluorouracil: Low **(Refer local policy)**

PREMEDICATIONS:

DOCEtaxel

- dexAMETHasone 8 mg PO twice daily for 3 days, starting one day prior to each DOCEtaxel administration unless contraindicated. Patient must receive minimum of 3 doses pre-treatment.
- ***Consideration may be given, at the discretion of the prescribing consultant, to the use of a single dose of dexAMETHasone 20mg IV immediately before chemotherapy where patients have missed taking the oral premedication dexAMETHasone as recommended by the manufacturer (6,7,)***

CISplatin

- Hydration prior and post CISplatin administration **(Reference local policy or see recommendations above)**

OTHER SUPPORTIVE CARE:

Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities. See comment above in dose modifications.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

- **Neutropenia:** Most frequent adverse reaction. Fever or other evidence of infection must be assessed promptly and treated appropriately. DOCEtaxel should be administered when the neutrophil count is > $1.5x10^9$cells/L.
- **Neutropenic Enterocolitis:** A number of cases of neutropenic enterocolitis have been reported in patients treated with DOCEtaxel in France (8). This is a known and rare side effect of DOCEtaxel which may affect up to one in 1,000 people.
- **Fluid Retention:** Dexamethasone premedication must be given to reduce the incidence and severity of fluid retention. It can also reduce the severity of the hypersensitivity reaction.
- **Hypersensitivity Reactions:** Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of DOCEtaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localized cutaneous reactions do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of DOCEtaxel and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with DOCEtaxel.
- **Extravasation:** DOCEtaxel causes pain and tissue necrosis if extravasated. (**Refer to local extravasation guidelines**).
- **Hepatic Dysfunction:** DOCEtaxel undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST) may lead to increased toxicity and usually requires a dose reduction
- **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.
- **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:

- Risk of drug interactions causing increased concentrations of DOCEtaxel with CYP3A inhibitors Patients should also be counselled with regard to consumption of grapefruit juice
- Risk of drug interactions causing decreased concentrations of DOCEtaxel with CYP3A inducers
- Avoid concurrent use of CISplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. 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
- Caution should be taken when using 5-Fluorouracil in conjunction with medications which may affect DPD activity
- Current drug interaction databases should be consulted for more information

REFERENCES:

1. Posner MR, Hershock DM et al. CISplatin and Fluorouracil Alone or with DOCEtaxel in Head and Neck Cancer. NEJM 2007;357: 1705-15.
2. Vermorken JB, Remenar E et al. CISplatin, Fluorouracil, and DOCEtaxel in Unresectable Head and Neck Cancer NEJM 2007;357:1695-1704.
3. Lorch JH et al. Induction chemotherapy with CISplatin and fluorouracil alone or in combination with DOCEtaxel in locally advanced squamous cell carcinoma of the head and neck: long term results of the TAX 324 randomised phase 3 trial. Lancet Oncol 2011;12 (2):153-9.
4. Nephrotoxicity Associated with CISplatin EviQ ID: 184 v.3 https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/prophylaxis-and-prevention/184-nephrotoxicity-associated-with-CISplatin
5. Portilla D et al. CISplatin nephrotoxicity. UptoDate Accessed Oct 2017 https://www.uptodate.com/contents/CISplatin-nephrotoxicity?source=search_result&search=CISplatin%20hydration&selectedTitle=1~150
6. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
7. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network
8. Chouhan et al. Single premedication dose of dexamethasone 20mg IV before DOCEtaxel administration. J Oncol Pharm Practice 2010;17(3):155–159
9. Rogers ES et al. Efficacy and safety of a single dose of dexamethasone pre DOCEtaxel treatment: The Auckland experience. Annals of Oncology (2014) 25 (suppl_4): iv517-iv541.
10. Fatal Neutropenic Enterocolitis With DOCEtaxel in France by Aude Lecrubier. Available at http://www.medscape.com/viewarticle/876014
11. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. 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
12. HPRA Direct Healthcare Professional Communication. 5-Fluorouracil (i.v.), capecitabine and tegafur containing products: Pre-treatment testing to identify DPD-deficient patients at increased risk of severe toxicity. Accessed Aug 2020. Available at: https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information-from-marketing-authorisation-holders-of-products-containing-5-fluorouracil-(i-v-)-capecitabine-and-tegafur-as-approved-by-the-hpra.pdf?sfvrsn=0
13. CISplatin 1mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics Accessed May 2020. Available at: http://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-081-001_13022020153905.pdf
14. Taxotere Summary of Product Characteristics. Accessed May 2020. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000073/WC500035264.pdf
15. Fluorouracil 50mg/ml Solution for injection or Infusion Summary of Product Characteristics Accessed May 2020. Available at:https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-091-001_10052019144741.pdf

Version	Date	Amendment	Approved By
1	02/05/2016		Prof Maccon Keane
2	03/05/2018	Applied new NCCP regimen template Updated treatment table, revised CISplatin hydration regimen recommendations and standardised dosing in renal and hepatic impairment	Prof Maccon Keane
3	09/10/2019	Updated exclusion criteria Amended recommended Dose modification for haematological toxicity	Prof Maccon Keane
4	13/05/2020	Updated exclusion criteria Dosing in renal and hepatic impairment for DOCEtaxel updated	Prof Maccon Keane
5	24/8/2020	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	09/09/2021	Clarification of requirement for non-PVC infusion bag only. Amended emetogenic potential.	Prof Maccon Keane
6a	21/11/2023	Formatting changes and grammatical corrections.	NCCP
6b	08/04/2024	Updated title.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.