FLOT Therapy-14 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of locally advanced (≥T2) and/or nodal positive (N+) resectable gastric adenocarcinoma	C16	00344a	Hospital
Treatment of locally advanced ((≥T2) and/or nodal positive (N+) resectable adenocarcinoma of the oesophagogastreal junction	C16	00344b	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.

DOCEtaxel, oxaliplatin, folinic acid and 5-Fluorouracil are administered on Day 1 of a 14 day cycle.
Four neoadjuvant cycles are administered prior to surgery over 8 weeks and four adjuvant cycles are administered post-surgery over 8 weeks.

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

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	DOCEtaxel	50mg/m^2	IV infusion	[a]250mL 0.9% NaCl over 60 minutes	Every 14 days
2	1	[b]Oxaliplatin	85mg/m^2	IV infusion	[c]500mL glucose 5% over 2 hours[d]	Every 14 days
3	1	Folinic Acid[e] (Calcium leucovorin)	200mg/m^2	IV infusion	250mL glucose 5% over 2 hours	Every 14 days
4	1	5-Fluorouracil[f]	2600mg/m^2	Continuous IV infusion	Over 24 hours in 0.9% NaCl	Every 14 days
Secondary prophylaxis with G-CSF is recommended for patients who experience febrile neutropenia or treatment interruptions because of neutropenia or leucopenia.						
[a]75-185mg dose use 250mL infusion bag. For doses> 185mg use 500mL infusion bag **Use non-PVC infusion bag.**						
[b]Oxaliplatin is incompatible with 0.9% NaCl. Do not piggyback or flush lines with normal saline [c]For oxaliplatin doses ≤ 104mg use 250ml glucose 5%. Oxaliplatin administration must always precede the administration of 5-Fluorouracil. Oxaliplatin may be given at the same time as Folinic Acid *(Calcium Leucovorin)* using a Y connector.						
[d]Increase infusion rate time for oxaliplatin to 4 – 6 hours in case of laryngopharyngeal dysaesthesia reaction.						
[e]Folinic Acid *(Calcium Leucovorin)* must be administered prior to 5-Fluorouracil. It enhances the effects of 5-Fluorouracil by increasing 5-Fluorouracil binding to the target enzyme thymidylate synthetase.						
[f]See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency						

ELIGIBILITY:

- Indications as above
- ECOG status 0-2
- Adequate haematological, renal and liver status

EXCLUSIONS:

- Hypersensitivity to DOCEtaxel, oxaliplatin, 5-Fluorouracil or any of the excipients
- Severe hepatic impairment
- Severe renal impairment (creatinine clearance < 30mL/min)
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency

USE with CAUTION:

- Peripheral neuropathy ≥ Grade 2

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- 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 liver profile prior to each cycle
- Evaluate for peripheral neuropathy every 2 cycles or 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:

- 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)		Platelets ($x 10^9$/L)		WBC ($x 10^9$/L)	Dose of DOCEtaxel and Oxaliplatin
≥1	and	≥ 100	**and**	≥ 3	100% Dose
Thrombocytopenia with bleeding					Dose reduce to 75%
Febrile neutropenia: First occurrence Second occurrence (despite use of G-CSF) Further occurrences					 Consider the use of G-CSF Dose reduce to 75% Dose reduce to 50%
G-CSF secondary prophylaxis recommended for patients who experience febrile neutropenia or treatment interruptions because of neutropenia or leucopenia					

Renal and Hepatic Impairment:

Table 2: Dose modification in renal and hepatic impairment

Drug	Renal impairment		Hepatic Impairment			
DOCEtaxel	No dose reduction necessary		See Table 3 below			
Oxaliplatin	**CrCl (mL/min)**	**Dose**	Little information available. Probably no dose reduction necessary. Clinical decision.			
	>30	Treat at normal dose and monitor renal function				
	<30	Contraindicated				
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.			

Table 3: Dose modification of DOCEtaxel in hepatic impairment

Alkaline Phosphatase		AST and/or ALT		Serum Bilirubin	Dose
> 2.5 ULN	and	> 1.5 ULN		</= ULN	100%
> 6 ULN	and/or	> 3.5 ULN (AST and ALT)	and	> ULN	Stop treatment unless strictly indicated and should be discussed with a Consultant.

Non-haematological toxicity:

Table 4: Dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
Grade >2 non-haematological toxicity First occurrence Second occurrence	 Decrease dose of all drugs to 75% Decrease dose of all drugs to 50%

Oxaliplatin induced neuropathy:

Table 5: Dose modification of oxaliplatin due to oxaliplatin induced neuropathy

***Peripheral neuropathy**	
Grade 2 present at start of cycle	Reduce oxaliplatin to 65mg/m^2
Grade 3	
• First occurrence	Reduce oxaliplatin to 65mg/m^2
• 2nd occurrence	Reduce oxaliplatin to 50mg/m^2
• Persistent	Discontinue oxaliplatin
Grade 4	Discontinue oxaliplatin

*Neuropathy may be partially or wholly reversible after discontinuation of therapy; patients with good recovery from Grade 3 (not Grade 4) neuropathy may be considered for re-challenge with oxaliplatin, with starting dose one level below that which they were receiving when neuropathy developed.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

DOCEtaxel: Low (**Refer to local policy)**
Oxaliplatin: Moderate (**Refer to local policy)**
5-Fluorouracil: Low (**Refer to local policy)**

PREMEDICATIONS:

- 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 (4,5)***

OTHER SUPPORTIVE CARE:

Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see 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.

- **Neutropenia:** Most frequent adverse reaction. Fever or other evidence of infection must be assessed promptly and treated appropriately. Frequent blood count monitoring should be conducted in all patients treated with DOCEtaxel.
- **Extravasation:** DOCEtaxel causes pain and tissue necrosis if extravasated. Oxaliplatin causes irritation if extravasated. (Refer to local extravasation guidelines).

DOCEtaxel

- **Neutropenic Enterocolitis:** A number of cases of neutropenic enterocolitis have been reported in patients treated with DOCEtaxel in France (7). This is a known and rare side effect of DOCEtaxel which may affect up to one in 1,000 people.
- **Hypersensitivity Reactions:** Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions of DOCEtaxel. 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. 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.

- **Fluid Retention:** Dexamethasone premedication must be given to reduce the incidence and severity of fluid retention with DOCEtaxel. It can also reduce the severity of the hypersensitivity reaction.

5-Fluorouracil

- **Gastrointestinal toxicity:** Patients treated with 5-Fluorouracil should be closely monitored for diarrhoea and managed appropriately.
- **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.

Oxaliplatin

- **Platinum Hypersensitivity**: Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin to such patients is contraindicated.
- **Laryngopharyngeal dysesthesia:** An acute syndrome of laryngopharyngeal dysesthesia occurs in 1% - 2% of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm. Symptoms are often precipitated by exposure to cold. Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome.

DRUG INTERACTIONS:

- Risk of drug interactions causing increased concentrations of DOCEtaxel with CYP3A inhibitors and decreased concentrations of DOCEtaxel with CYP3A inducers.
- 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	18/08/2017		Prof Maccon Keane
2	04/10/2017	Amended dose modifications for haematological toxicity	Prof Maccon Keane
3	24/04/2019	Updated treatment table Amended adverse effects/regimen specific complications for DOCEtaxel. Updated hepatic dose modification and emetogenic potential.	Prof Maccon Keane
4	13/02/2020	Standardisation of treatment table. Update of exclusions and drug interaction. Update of recommended dose modifications for oxaliplatin in renal impairment.	Prof Maccon Keane
5	26/02/2020	Standardisation of treatment table.	Prof Maccon Keane
6	19/08/2020	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
7	28/04/2021	Reviewed	Prof Maccon Keane
8	09/09/2021	Clarification of requirement for non-PVC infusion bag only	Prof Maccon Keane
8a	21/11/2023	Formatting changes and grammaticalcorrections.	NCCP
8b	25/02/2025	Additional wording added to baseline testing section.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.