Gemcitabine and DOCEtaxel Therapy[i] - 21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of locally advanced unresectable or metastatic soft tissue sarcoma.	C49	00501a	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.

Gemcitabine is administered on Day 1 and Day 8 and DOCEtaxel on Day 8 of a 21-day cycles for up to 6 cycles or until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1, 8	Gemcitabine	675mg/m^2	IV	250ml 0.9% NaCl over 90 minutes	Every 21 days for up to six cycles
2	8	[a]DOCEtaxel	75mg/m^2	IV	250ml 0.9% NaCl over 60 minutes	Every 21 days for up to six cycles
[a]Concentration of final volume should be <0.74mg/ml Use non-PVC infusion bag.						

ELIGIBILITY:

- Indication as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to DOCEtaxel, gemcitabine or any of the excipients
- Pregnancy
- Breast feeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile

- Bone profile

Regular tests:

- FBC, renal and liver profile prior to each cycle

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other tests as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

Table 1: Dose reduction levels for gemcitabine and DOCEtaxel

Starting Dose	Gemcitabine 675mg/m^2	DOCEtaxel 75mg/m^2
Level -1	540 mg/m^2	60 mg/m^2
Level -2	450 mg/m^2	50 mg/m^2
Level-3	Discontinue	Discontinue

Haematological:

Table 2: Dose modifications for haematological toxicity

Day	ANC (x10^9/L)		Platelets (x10^9/L)	Dose
1	≥1	And	≥100	100%
	<1	and/or	<100	Delay for 1 week or until recovery
8	≥1	and	≥75	100%
	<1	and/or	<75	Delay for one week, if recovered sufficiently by day 15, the gemcitabine and DOCEtaxel can be administered but with a dose reduction as indicated in the table 1 for all subsequent cycles
Febrile Neutropenia **1st occurrence** **2nd occurrence**				Hold chemotherapy for remainder of cycle and consider addition of GCSF to subsequent cycles. Consider dose reduction by 1 dose level (Table 1)

Renal and Hepatic Impairment:

Table 3: Dose modifications in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment					
DOCEtaxel	No data available in patients with severely impaired renal function		**Serum Bilirubin**		**AST and/or ALT**		**Alkaline Phosphatase**	**Dose**
					> 1.5 ULN	and	> 2.5 ULN	75 mg/m2
			> ULN	and/or	> 3.5 ULN (AST and ALT)	and	> 6 ULN	Stop treatment unless strictly indicated and should be discussed with a Consultant.
Gemcitabine	**Cr Cl (ml/min)**	**Dose**	AST elevations do not seem to cause dose limiting toxicities.					
	>30	100%						
	<30	Consider dose reduction. Clinical decision						

Management of adverse events:

Table 4: Dose Modifications for Adverse Events

Adverse reactions	Recommended dose modification
Grade 2 peripheral neuropathy 1st occurrence 2nd occurrence	 Reduce dose of gemcitabine and DOCEtaxel by 1 dose level Reduce dose of gemcitabine and DOCEtaxel by 1 dose level
Grade ≥3 Non haematological toxicities	Withhold treatment until toxicity resolved to Grade ≤1 and then reduce dose by 1 level

SUPPORTIVE CARE:

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

PREMEDICATIONS:

- Dexamethasone 8 mg PO twice daily for 3 days, starting one day prior to each DOCEtaxel administration (day 7) 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 (5,6)*

OTHER SUPPORTIVE CARE:

Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities G-CSF

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.

Gemcitabine

- Renal Toxicity: Irreversible renal failure associated with hemolytic uremic syndrome may occur (rare) with gemcitabine. Use caution with pre-existing renal dysfunction.
- Pulmonary Toxicity: Acute shortness of breath may occur with gemcitabine. Discontinue treatment with gemcitabine if drug-induced pneumonitis is suspected.
- Cardiovascular: Due to the risk of cardiac and/or vascular disorders with gemcitabine, particular caution must be exercised with patients presenting a history of cardiovascular events.

DOCEtaxel

- **Fluid Retention**: Dexamethasone premedication must be given prior to administration of DOCEtaxel 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.

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
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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2. University College London. GeDDiS: A prospective randomised controlled phase III trial of gemcitabine and docetaxel compared with doxorubicin as first line treatment in previously untreated advanced unresectable or metastatic soft tissue sarcomas [Internet]. Available from: https://www.ctc.ucl.ac.uk/TrialDocuments/Uploaded/GeDDiS%20Protocol%20v8.0%2022Mar2016_06062017_0.pdf
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8. Gemcitabine 40 mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics Accessed July 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-039-005_13022020104725.pdf

Version	Date	Amendment	Approved By
1	13/08/2018		Dr Michael McCarthy
2	30/07/2020	Standardisation of treatment table Updated exclusion criteria Standardisation of pre-medication Updated adverse events section	Prof Maccon Keane
3	09/09/2021	Clarification of requirement for non-PVC infusion bag only	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this indication 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 aware of their responsibility in communicating any relevant information to the patient and also in 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.