Gemcitabine (1000mg/m^2) and Capecitabine (650mg/m^2) Therapy - 21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement Status*
Locally advanced or metastatic pancreatic carcinoma[i]	C25	00384a	N/A
Locally advanced biliary tree carcinoma[ii]	C23	00384b	

*This applies to post 2012 indications

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 individual clinical circumstances.

Gemcitabine is administered on day 1 and day 8 and capecitabine is taken on day 1-14 of a 21-day cycle until disease progression or unacceptable toxicity.

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

Day	Drug	Dose	Route	Diluent & Rate
1 and 8	Gemcitabine	1000mg/m^2	IV infusion	250mL NaCl 0.9% over 30 minutes
1 - 14	Capecitabine	650mg/m^2 Twice Daily[a, b, c, d]	PO with food	N/A
[a]The dose to be administered should consider the available tablet strengths. Please refer to the NCCP DOSE BANDING TABLES for guidance on dosing of capecitabine - Available on the NCCP website Tablets should be swallowed whole with plenty of water with food or within 30 minutes of eating. Tablets should not be crushed or cut. [b](Total daily dose = 1300mg/m^2)				
[c] See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency				
[d] Capecitabine is commonly available as 150mg and 500mg film-coated tablet				

ELIGIBILITY:

- Indication as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to gemcitabine, capecitabine or any of the excipients
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency
- History of severe and unexpected reactions to fluoropyrimidine therapy
- Pregnancy
- Breastfeeding
- Severe hepatic or renal impairment associated with capecitabine

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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 capecitabine using phenotype and/or genotype testing unless patient has been previously tested
    - In patients with moderate or severe renal impairment, blood uracil levels used 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:

- Day 1: FBC, renal and liver profile
- Day 8: FBC
- Assessment of hands and feet for palmar-plantar erythrodysaesthesia (PPE) 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:

Prior to commencing a new treatment cycle (i.e. day 1), ANC must be ≥1 x 10^9/L and platelets ≥ 100 x10^9/L.

Table 1: Dose modifications for gemcitabine and capecitabine within a cycle

ANC (x 10^9 /L)		Platelet count (x 10^9 /L)		Other toxicity	Recommended dose of Gemcitabine	Recommended dose of Capecitabine
≥1	and	≥100			100 %	100%
0.5- 1	or	50-100			75%	100%
< 0.5	or	<50			Omit. Do not restart treatment until ANC ≥ 0.5 and platelets ≥ 50	Interrupt treatment until recovery of toxicity to ≤ Grade 1
ANC < 0.5 for ≥ 5 days **or** ANC < 0.1 for ≥ 3 days **or** Any incidence of febrile neutropenia	**or**	< 25	**or**	cycle delay of >1 week due to any toxicity	Reduce dose to 75% of the original cycle initiation dose for all subsequent cycles.	Interrupt treatment until recovery of toxicity to ≤ Grade 1

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Renal and hepatic impairment:

Table 2: Dose modifications for capecitabine and gemcitabine in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
Gemcitabine	**CrCl (mL/min)**	**Dose**	**Total bilirubin (micromol/L)**	**Dose**
	≥30	No dose adjustment is needed	<27	No dose adjustment is needed
	<30	No need for dose adjustment is expected	≥27	Either start at 80% of the original dose and increase the dose if tolerated or start with full dose with active monitoring.
	Haemodialysis	No need for dose adjustment is expected. Start haemodialysis 6-12 hours after administration.		
Capecitabine	**CrCl (mL/min)**	**Dose**	*No need for dose adjustment is needed	
	51-80	No dose adjustment is needed		
	30-50	75% of the original dose		
	<30	Not recommended		
	Haemodialysis	Not recommended		
Renal and hepatic recommended as per Giraud et al 2023. *Reference Table 7 for dose modification of capecitabine in treatment related hepatotoxicity				

Management of adverse events:

Table 3: Dose Modification of gemcitabine for Adverse Events

Adverse reactions	Recommended dose modification of gemcitabine
Grade ≥ 2 Pneumonitis	Discontinue gemcitabine
Grade > 3 Non-haematological toxicity (except nausea/vomiting)	Therapy with gemcitabine should be withheld (until toxicity has resolved to grade ≤ 1) and may be resumed with 50% dose reduction or treatment discontinued at discretion of prescribing consultant.
Grade > 4 Non-haematological toxicity	Discontinue treatment
• Severe cutaneous adverse reactions (SCARs) e.g. Stevens-Johnson syndrome (SJS) ,toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP) • Pulmonary toxicity • Haemolytic syndrome	Discontinue gemcitabine

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Table 4: Dose Modification of Capecitabine for Adverse Events

Toxicity grades*	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2	Interrupt until resolved to grade 0-1	
• 1st appearance		100%
• 2nd appearance		75%
• 3rd appearance		50%
• 4th appearance	Discontinue permanently	
Grade 3	Interrupt until resolved to grade 0-1	
• 1st appearance		75%
• 2nd appearance		50%
• 3rd appearance	Discontinue permanently	
Grade 4	Discontinue permanently **or**	
• 1st appearance	If consultant deems it to be in patient's best interest to continue, interrupt until resolved to grade 0-1	50%
• 2nd appearance	Discontinue permanently	
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. *Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.		

Table 5: Dose Modification of capecitabine for diarrhoea

Grade	Diarrhoea	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
0-1	Increase of 2 to 3 stools/day or nocturnal stools	Maintain dose level	Maintain dose level
2	Increase of 4 to 6 stools/day or nocturnal stools		
	• 1st appearance	Interrupt until resolved to grade 0-1	100%
	• 2nd appearance		75%
	• 3rd appearance		50%
	• 4th appearance	Discontinue permanently	
3	Increase of 7 to 9 stools/day or incontinence		
	• 1st appearance	Interrupt until resolved to grade 0-1	75%
	• 2nd appearance		50%
	• 3rd appearance	Discontinue permanently	
4	Increase of 10 or more stools/day or grossly bloody diarrhoea; may require parenteral support		
	• 1st appearance	Discontinue permanently **or** If consultant deems it to be in patient's best interest to continue, interrupt until resolved to grade 0-1	50%
	• 2nd appearance	Discontinue permanently	
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			

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Hand foot syndrome:

Table 6: Dose modification of capecitabine in hand foot syndrome

Toxicity Grade		Dose Modification
Grade 1	Skin changes (e.g., numbness, dysesthesia, paraesthesia, tingling, erythema) with discomfort not disrupting normal activities.	100% Dose
Grade 2	Skin changes (e.g., erythema, swelling) with pain affecting activities of daily living.	Withhold treatment until event resolves or decreases in intensity to grade 1.
Grade 3	Severe skin changes (e.g., moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living.	Withhold treatment until event resolves or decreases in intensity to grade 1. Subsequent doses of capecitabine should be decreased.

Treatment related hepatotoxicity

Table 7: Dose modification of capecitabine in treatment related hepatotoxicity

Bilirubin		ALT, AST	Dose Modification
> 3.0 x ULN	**or**	> 2.5 x ULN	Withhold treatment until bilirubin decreases to ≤ 3.0 x ULN or ALT, AST decrease to ≤ 2.5 x ULN

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

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

Capecitabine: Minimal to low **(Refer to local policy)**

For information:
Within NCIS regimens, antiemetics have been standardised by the 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 the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS: Not usually required

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) **(Refer to local policy)**
- Diarrhoea and dehydration: This may be dose limiting with capecitabine therapy. Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated **(Refer to local policy)**

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ADVERSE EFFECTS:

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

REGIMEN SPECIFIC COMPLICATIONS:

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

Gemcitabine:

- **Pulmonary Toxicity**: Acute shortness of breath may occur. 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
- **Haemolytic Uraemic syndrome:** Irreversible renal failure associated with hemolytic uremic syndrome may occur (rare) with Gemcitabine. Use caution with pre-existing renal dysfunction

Capecitabine:

- **Cardiotoxicity:** Angina-like chest pain, tachycardia, arrhythmias, heart failure, myocardial infarction and cardiac arrest may occur with capecitabine especially in patients with a prior history of coronary artery disease
- **Dihydropyrimidine dehydrogenase (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

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information

REFERENCES:

1. Knox J, Hedley D, Oza A. et al. Combining Gemcitabine and Capecitabine in Patients with Advanced Biliary Cancer: A phase 11 Trial. Journal of Clinical Oncology 2005;23(10), 2332-2338
2. 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/
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V6 2025. 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
4. HPRA Direct Healthcare Professional Communication. 5-Fluorouracil (i.v.), capecitabine and tegafur containing products: Pre-treatment testing to identify DPD-deficient patients at increased

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5. Gemcitabine 40 mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics Last updated:14/12/2023 Accessed Sept 2025. Available at: https://assets.hpra.ie/products/Human/27418/Licence_PA1986-122-001_14122023101810.pdf
6. Capecitabine (Xeloda®) Summary of Product Characteristics. Last updated:02/05/2025 Accessed Aug 2025. Available at: https://www.ema.europa.eu/en/documents/product-information/xeloda-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	20/12/2016		Prof Maccon Keane
2	10/09/2018	Applied new NCCP regimen template. Updated title and exclusions with respect to DPD deficiency.	Prof Maccon Keane
3	17/10/2018	Standardisation of dose modification tables (hematological, renal and hepatic modifications and adverse events). Inclusion of dose modification tables for capecitabine.	Prof Maccon Keane
4	11/03/2020	Updated capecitabine dosing in renal impairment.	Prof Maccon Keane
5	26/08/2020	Reviewed. 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	18/01/2023	Updated dose modification for gemcitabine in hepatic impairment. Amended emetogenic potential.	Prof Maccon Keane
6a	03/03/2025	Additional wording added to baseline testing section.	NCCP
7	20/10/2025	HSE approved reimbursement status updated. Regular testing updated. Treatment section, Emetogenic potential, drug interactions updated in line with NCCP standardisation. Renal and hepatic dose modifications table updated as per Giraud et al 2023.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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[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.
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/

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