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

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Locally advanced or metastatic pancreatic carcinoma	C25	00384a	Gemcitabine – Hospital Capecitabine - CDS
Locally advanced biliary tree carcinoma	C23	00384b	

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 capecitabine is taken on day 1-14 of a 21 day cycle until disease progression or unacceptable toxicity develops.

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

Day	Drug	Dose	Route	Diluent & Rate
1 and 8	Gemcitabine	1000mg/m^2	IV infusion	250ml NaCl 0.9% over 30mins
1 - 14	Capecitabine	650mg/m^2 Twice Daily[a, b, c]	PO with food	N/A
[a] The dose to be administered should consider the available tablet strengths. Reference the NCCP DOSE BANDING TABLES here for guidance on dosing of capecitabine. 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 DPD deficiency.				

ELIGIBILITY:

- Indications as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to gemcitabine, capecitabine or any of the excipients
- Known complete DPD deficiency
- History of severe and unexpected reactions to fluoropyrimidine therapy
- Pregnancy and lactation
- Severe hepatic or renal impairment

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

Regular tests:

- Day 1: FBC, renal and liver profile
- Day 8: FBC

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

Renal and hepatic impairment:

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

Drug	Renal Impairment		Hepatic Impairment
Capecitabine*	**Creatinine Clearance (CrCl ml/min)**	**Dose**	In the absence of safety and efficacy data in patients with hepatic impairment, capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis.
	≥30	100%	
	<30	Omit	
Gemcitabine	≥ 30	100%	If bilirubin ≥27 micromol/L, use dose of 800 mg/m2 and increase dose to full dose if tolerated.
	<30	Consider dose reduction – clinical decision.	
*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

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 • 1st appearance	Interrupt until resolved to grade 0-1	100%
• 2nd appearance		75%
• 3rd appearance		50%
• 4th appearance	Discontinue permanently	
Grade 3 • 1st appearance	Interrupt until resolved to grade 0-1	75%
• 2nd appearance		50%
• 3rd appearance	Discontinue permanently	
Grade 4 • 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		

*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			

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:

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

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

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).**

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**: Fever or other evidence of infection must be assessed promptly and treated appropriately.

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:

- **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.
- **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 fluorouracil may improve clinical outcomes in patients receiving continuous 5-fluorouracil infusions.

- **Hand-foot syndrome (HFS)**: HFS, also known as palmar-plantar erythrodysaesthesia (PPE), is a common side effect associated with capecitabine (see Table 6 for dose modification of capecitabine for HFS).

DRUG INTERACTIONS:

- Capecitabine enhances the anticoagulant effect of warfarin. Patients taking coumarin derivative anticoagulants should be monitored regularly for alterations in their coagulation parameters and the anti-coagulant dose adjusted accordingly.
- Sorivudine inhibits dihydropyrimidine dehydrogenase thus increasing its toxicity. Therefore capecitabine must not be administered concomitantly with sorivudine or its chemically related analogues.
- Patients taking phenytoin or fosphenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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3. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V4 2022. 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. 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
6. Gemcitabine 40 mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics Accessed Sept 2020. Available at: http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0405-080-001_08092015123059.pdf
7. Capecitabine (Xeloda®) Summary of Product Characteristics. Accessed Sept 2020. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000316/WC500058151.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

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