Capecitabine and Temozolomide Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved Reimbursement Status*
Treatment of patients with locally advanced or metastatic neuroendocrine tumours of the pancreas[i]	C24, C25	00505a	N/A

*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 patients individual clinical circumstances.

Capecitabine is administered twice daily for 14 days (days 1-14) followed by a 14 day rest period on days 15-28.
Temozolomide is administered once daily on 5 consecutive days from day 10-14 of a 28 day cycle for a total of 6 cycles unless the patient experiences disease progression or unacceptable toxicity.

Day	Drug	Dose	Route	Cycle
1-14	Capecitabine	750mg/m^2 Twice daily[a, b, c]	PO with food	Every 28 days
10-14	Temozolomide	200mg/m^2 Once daily	PO[d]	Every 28 days
[a]The dose to be administered should consider the available tablet strengths. Please refer to the NCCP DOSE BANDING TABLES for dosing of capecitabine (Available on NCCP website). 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 = 1500mg/m^2)				
[c]See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency.				
[d]Temozolomide hard capsules should be administered in the fasting state. The capsules must be swallowed whole with a glass of water and must not be opened or chewed. If vomiting occurs after the dose is administered, a second dose should not be administered that day.				
Capecitabine is commonly available in 150mg and 500mg film-coated tablets.				
Temozolomide is commonly available in 5mg/20mg/100mg/140mg/180mg and 250mg hard capsules.				

ELIGIBILITY:

- Indication as above
- ECOG status 0-1

EXCLUSIONS:

- Hypersensitivity to capecitabine, temozolomide or any of the excipients
- Hypersensitivity to dacarbazine (temozolomide contraindicated)
- Known complete DPD deficiency
- History of severe and unexpected reactions to fluoropyrimidine therapy
- Pregnancy or breastfeeding
- Severe leucopenia, neutropenia or thrombocytopenia
- Severe hepatic or renal impairment (creatinine clearance below 30 mL/min at baseline)
- Recent or concomitant treatment with brivudine

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- INR tests if patient is on warfarin as clinically indicated
- Virology screen - Hepatitis B (HBsAg, HBcoreAb)
  *(Reference Regimen Specific Complications for information on Hepatitis B reactivation)
- 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 for 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
- INR tests if patient is on warfarin 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:

- Any dose modification should be discussed with a Consultant
- Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction)
- Once the dose has been reduced, it should not be increased at a later time
- For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening, e.g. alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption
- Patients taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs
- Doses of capecitabine omitted for toxicity are not replaced
- 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

Haematological:

- Initiation of treatment with capecitabine in patients with baseline neutrophil counts $<1.5x10^9$/L and/or thrombocyte counts of $<100 \times 10^9$/L should be undertaken with caution
- If unscheduled laboratory assessments during a treatment cycle show that the neutrophil count drops below $1x10^9$/L or that the platelet count drops below $75x10^9$/L, treatment with capecitabine should be interrupted

Table 1: Dose modification of capecitabine and temozolomide based on haematological toxicity

ANC ($x 10^9$/L)		Platelets($x 10^9$/L)	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose
≥ 1.5	and	≥ 75	100%	100%	100%	100%
1-1.49	or	50 – 74.9	Delay* then 100%	Delay* then 75%	Delay* then 50%	Discontinue
0.5-0.99	or	25- 49.9	Delay* then 75%	Delay* then 50%	Discontinue	Discontinue
< 0.5	or	< 25	Discontinue or delay* then 50%	Discontinue	Discontinue	Discontinue

*Delay until ANC ≥ 1.5x 10^9/L and platelets ≥ 75x10^9/L

Renal and Hepatic Impairment:

Table 2: Dose modifications in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
Capecitabine	**CrCl (mL/min)**	**Dose**	**Impairment level:**	**Dose**
	51-80	No dose adjustment is needed	*No dose adjustment is needed	
	30-50	75% of the original dose		
	<30	Not recommended		
	Haemodialysis	Not recommended		
Temozolomide	**CrCl (mL/minute)**	**Dose**	**Impairment level:**	**Dose**
	≥ 36	No dose adjustment is needed	Child-Pugh A/B:	No dose adjustment is needed
	< 36	No need for dose adjustment is expected	Child-Pugh C:	No need for dose adjustment is expected
	Haemodialysis	No need for dose adjustment expected		
Renal and hepatic recommended as per Giraud et al 2023. *Reference Table 6 for dose modification of capecitabine in treatment related hepatotoxicity				

Management of adverse events:

Table 3 shows the recommended dose modifications of capecitabine for those toxicities which are not individually specified:

Table 3: Capecitabine dose reduction schedule based on toxicity (Any)

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 4: 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 5: 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 6: 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 x ULN or ALT, AST decrease to ≤ 2.5 x ULN

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

Capecitabine: Minimal - Low **(Refer to local policy)**
Temozolomide: Moderate - High (**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: None usually required

OTHER SUPPORTIVE CARE:

- Medication may be required for management of diarrhea related to capecitabine, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see local policy
- PJP prophylaxis **(Refer to local policy)**
- Palmar-plantar erythrodysaesthesia (PPE) prevention

ADVERSE EFFECTS:

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

REGIMEN SPECIFIC COMPLICATIONS:

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

Temozolomide

- **Opportunistic infections and reactivation of infections**: Opportunistic infections (such as Pneumocystis jirovecii pneumonia) and reactivation of infections (such as HBV, CMV) have been observed during the treatment with temozolomide
- **Pneumocystis jirovecii pneumonia (PJP):** Patients who received concomitant temozolomide and RT in a pilot trial for the prolonged 42-day schedule were shown to be at particular risk for developing PJP. There may be a higher occurrence of PJP when temozolomide is administered during a longer dosing regimen. However, all patients receiving temozolomide, particularly patients receiving steroids, should be observed closely for the development of PJP, regardless of the regimen. Cases of fatal respiratory failure have been reported in patients using temozolomide, in particular in combination with dexamethasone or other steroids
- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy **(Refer to local infectious disease policy**). These patients should be considered for assessment by hepatology
- **Hepatotoxicity:** Hepatic injury, including fatal hepatic failure, has been reported in patients treated with temozolomide. Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal hepatic failure. For all patients, liver function tests should be checked after each treatment cycle. For patients with significant liver function abnormalities, physicians should assess the benefit/risk of continuing treatment. Liver toxicity may occur several weeks or more after the last treatment with temozolomide

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information

REFERENCES:

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2. BCCA Protocol Summary for Palliative Therapy of Metastatic Neuroendocrine Cancer using Temozolomide and Capecitabine GIAVTZCAP- Oct 1 2016.
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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 risk of severe toxicity. Last updated Oct 2024. Accessed Sept 2025 Available at: https://assets.hpra.ie/data/docs/default-source/product-updates/dhpc/human-medicines/label-for-dhpcs/medicines-containing-5-fluorouracil-(i-v-)---direct-healthcare-professional-communication-october-2024.pdf?sfvrsn=77aa96a6_1
5. 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/
6. 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
7. Capecitabine (Xeloda®) Summary of Product Characteristics. Last updated 05/05/2025. Accessed Sept 2025. Available at: https://www.ema.europa.eu/en/documents/product-information/xeloda-epar-product-information_en.pdf
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Version	Date	Amendment	Approved By
1	13/08/2018		Prof Maccon Keane
2	11/03/2020	Updated dose modifications for capecitabine in renal impairment.	Prof Maccon Keane
3	23/09/2020	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 Updated wording regarding Hepatitis B reactivation	Prof Maccon Keane
4	18/01/2023	Amended emetogenic potential	Prof Maccon Keane
4a	03/03/2025	Updated wording in baseline testing section.	NCCP
5	11/11/2025	HSE approved reimbursement Status updated. ECOG status updated. Treatment section, Emetogenic potential, drug interactions updated in line with NCCP standardisation. Renal and hepatic impairment table updated as per Giraud et al 2023.	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.