

## Capecitabine and Temozolomide Therapy<sup>1</sup>

### INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of patients with locally advanced or metastatic neuroendocrine tumours of the pancreas	C25	00505a	CDS

### 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's 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 6 cycles or until disease progression or unacceptable toxicity develops.

Day	Drug	Dose	Route	Cycle
1-14	Capecitabine	750mg/m <sup>2</sup> Twice daily <sup>a, b, c</sup>	PO with food	Every 28 days for 6 cycles
10-14	Temozolomide	200mg/m <sup>2</sup> Once daily	PO <sup>d</sup>	Every 28 days for 6 cycles

<sup>a</sup>The dose to be administered should consider the available tablet strengths. Reference to the NCCP DOSE BANDING TABLES for dosing of capecitabine [here](#). 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.

<sup>b</sup>(Total daily dose = 1500mg/m<sup>2</sup>)

<sup>c</sup>See dose modifications section for patients with identified partial DPD deficiency.

<sup>d</sup>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.

### ELIGIBILITY:

- Indications 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 and lactation
- Severe leucopenia, neutropenia or thrombocytopenia
- Severe hepatic impairment
- Severe renal impairment (creatinine clearance below 30 ml/min [Cockcroft and Gault] at baseline)

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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
- INR tests if patient is on warfarin as clinically indicated
- DPD testing prior to first treatment with capecitabine using phenotype and/or genotype testing unless patient has been previously tested
- Virology screen - Hepatitis B (HBsAg, HBcoreAb)  
\*(Reference Adverse Events/Regimen Specific Complications for information on Hepatitis B reactivation)

### 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  $<1.5 \times 10^9/L$  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  $1 \times 10^9/L$  or that the platelet count drops below  $75 \times 10^9/L$ , treatment with capecitabine should be interrupted.

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

ANC (x 10 <sup>9</sup> /L)		Platelets(x 10 <sup>9</sup> /L)	1 <sup>st</sup> Event Dose	2 <sup>nd</sup> Event Dose	3 <sup>rd</sup> Event Dose	4 <sup>th</sup> 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<sup>9</sup>/L and platelets ≥ 75x10<sup>9</sup>/L

### Renal and Hepatic Impairment:

**Table 2: Dose modifications in renal and hepatic impairment**

Drug	Renal Impairment		Hepatic Impairment
Capecitabine	<b>Cr Cl (ml/min)</b>	<b>Dose</b>	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% dose	
	<30	Discontinue treatment	
Temozolomide	<p>No data are available on the administration of temozolomide in patients with renal impairment.</p> <p>Caution should be exercised when temozolomide is administered in these patients.</p>		<p>The pharmacokinetics of temozolomide were comparable in patients with normal hepatic function and in those with mild or moderate hepatic impairment.</p> <p>No data are available on the administration of temozolomide in patients with severe hepatic impairment (Child’s Class C).</p> <p>Based on the pharmacokinetic properties of temozolomide, it is unlikely that dose reductions are required in patients with severe hepatic impairment. However, caution should be exercised when temozolomide is administered in these patients.</p>

\*Reference Table 6 - for dose modification of capecitabine in treatment related hepatotoxicity

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## 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)
<b>Grade 1</b>	Maintain dose level	Maintain dose level
<b>Grade 2</b>	Interrupt until resolved to grade 0-1	100%
• 1 <sup>st</sup> appearance		75%
• 2 <sup>nd</sup> appearance		50%
• 3 <sup>rd</sup> appearance		
• 4 <sup>th</sup> appearance	Discontinue permanently	
<b>Grade 3</b>	Interrupt until resolved to grade 0-1	75%
• 1 <sup>st</sup> appearance		50%
• 2 <sup>nd</sup> appearance		
• 3 <sup>rd</sup> appearance	Discontinue permanently	
<b>Grade 4</b>	Discontinue permanently or If consultant deems it to be in patient's best interest to continue, interrupt until resolved to grade 0-1	50%
• 1 <sup>st</sup> appearance		
• 2 <sup>nd</sup> 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.

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**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	Interrupt until resolved to grade 0-1	
	• 1 <sup>st</sup> appearance		100%
	• 2 <sup>nd</sup> appearance		75%
	• 3 <sup>rd</sup> appearance	50%	
	• 4 <sup>th</sup> appearance	Discontinue permanently	
3	Increase of 7 to 9 stools/day or incontinence	Interrupt until resolved to grade 0-1	
	• 1 <sup>st</sup> appearance		75%
	• 2 <sup>nd</sup> appearance	50%	
	• 3 <sup>rd</sup> appearance	Discontinue permanently	
4	Increase of 10 or more stools/day or grossly bloody diarrhoea; may require parenteral support		
	• 1 <sup>st</sup> 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%
	• 2 <sup>nd</sup> 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

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## SUPPORTIVE CARE:

### EMETOGENIC POTENTIAL:

- Capecitabine: Minimal - Low (**Refer to local policy**).  
 Temozolomide: Moderate - High (**Refer to local policy**).

**PREMEDICATIONS:** Not 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**).

## 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.

### Capecitabine

- **Diarrhoea and dehydration:** This may be dose limiting. 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 erythrodysesthesia (PPE), is a common side effect associated with capecitabine (see Table 5 above for dose modification of capecitabine for HFS).

### 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

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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:

- 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.
- No studies have been conducted to determine the effect of temozolomide on the metabolism or elimination of other medicinal products.
- Since temozolomide does not undergo hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products.
- Current drug interaction databases should be consulted for more information.

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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 erythrodysesthesia Updated wording regarding Hepatitis B reactivation	Prof Maccon Keane
4	18/01/2023	Amended emetogenic potential	Prof Maccon Keane

Comments and feedback welcome at [oncologydrugs@cancercontrol.ie](mailto:oncologydrugs@cancercontrol.ie).

<sup>i</sup> 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.

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