Pembrolizumab 200mg, CISplatin 80mg/m^2 and 5-Fluorouracil Infusional Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved Reimbursement Status*
Pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy, for the first line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with CPS≥10[i]	C15/C16	00739a	Pembrolizumab: ODMS 01/06/2023 CISplatin: N/A 5-Fluorouracil: N/A

*This applies to post 2012 indications only

Note: As the platinum and fluoropyrimidine based chemotherapy is not defined in the EMA licensed indication other evidence based platinum and fluoropyrimidine regimens may be used in combination with pembrolizumab.

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.

Pembrolizumab and CISplatin are administered on Day 1; 5-Fluorouracil 800 mg/m^2 per day is given by continuous intravenous (IV) infusion on Days 1–5 of each cycle, as detailed in Table 1. Alternatively, 5-Fluorouracil may be administered at a dose of 1000 mg/m^2 per day given by continuous IV infusion on Days 1–4 of each cycle as detailed in Table 2 below.

CISplatin should be administered for up to a maximum of 6 cycles. Treatment with pembrolizumab and 5-Fluorouracil is administered until disease progression or unacceptable toxicity develops.

Each cycle is 21 days.

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

Table 1: Treatment schedule for Pembrolizumab 200mg, CISplatin 80mg/m^2 and 5-Fluorouracil 800mg/m^2/day Days 1-5

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pembrolizumab [1]	200mg	IV infusion	100mL 0.9% NaCl over 30 minutes [2]	Every 21 days
2	1	CISplatin	80mg/m^2	IV Infusion	1000mL NaCl 0.9% over 1 hour [3, 4]	Every 21 days, **cycles 1 - 6**
3	1-5	5-Fluorouracil [5]	800mg/m^2/day (total dose = 4000mg/m^2 over 120 hours)	Continuous IV infusion over 5 days	Infusor pump	Every 21 days

[1] Pembrolizumab is diluted to a final concentration ranging from 1-10mg/mL.

[2] Administer using a low-protein binding 0.2 to 5 micrometre in-line or add-on filter.

[3] **Pre and post hydration therapy required for CISplatin**
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:
- Administer 10mmol magnesium sulphate (MgSO4) ((+/-KCl 10-20mmol/L if indicated) in 1000 mL NaCl 0.9% over 60 -120 minutes. (Refer to relevant local hospital policy for advice on administration of electrolyte infusions).

Administer CISplatin as described above.
Post hydration: Administer 1000 mL 0.9% NaCl over 60 minutes.

[4] Mannitol 10% may be used as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload.

[5] See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

Table 2: Alternate Treatment schedule for Pembrolizumab 200mg, CISplatin 80mg/m^2 and 5-Fluorouracil 1000mg/m^2/day Days 1-4

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pembrolizumab [1]	200mg	IV infusion	100mL 0.9% NaCl over 30 minutes [2]	Every 21 days
2	1	CISplatin	80mg/m^2	IV Infusion	1000mL NaCl 0.9% over 1 hour [3, 4]	Every 21 days, **cycles 1-6**
3	1-4	5-Fluorouracil [5]	1000mg/m^2/day (total dose = 4000mg/m^2 over 96 hours)	Continuous IV infusion over 4 days	Infusor pump	Every 21 days

[1] Pembrolizumab is diluted to a final concentration ranging from 1-10mg/mL.

[2] Administer using a low-protein binding 0.2 to 5 micrometre in-line or add-on filter.

[3] **Pre and post hydration therapy required for CISplatin**
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:
- Administer 10mmol magnesium sulphate (MgSO4) ((+/-KCl 10-20mmol/L if indicated) in 1000 mL NaCl 0.9% over 60-120 minutes. (Refer to relevant local hospital policy for advice on administration of electrolyte infusions).

Administer CISplatin as described above.
Post hydration: Administer 1000 mL 0.9% NaCl over 60 minutes.

[4] Mannitol 10% may be used as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload.

[5] See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

- Indication as above
- Histologically or cytologically confirmed locally advanced unresectable or metastatic oesophageal carcinoma or gastro-oesophageal junction (GEJ) carcinoma (Siewert Type 1)
- Aged ≥ 18 years
- ECOG status 0-2
- PD-L1 with a combined positive score (CPS) >10 as demonstrated by a validated assay method
- Adequate organ function

CAUTION:

- History of serious autoimmune disease
- Immunosuppressive doses of systemic corticosteroids or other immunosuppressive medication(s) (defined as >10mg prednisoLONE/daily (or steroid equivalent, excluding inhaled or topical steroids)
- Any active clinically significant infection requiring therapy
- Active or unstable CNS metastases

EXCLUSIONS:

- Hypersensitivity to pembrolizumab, CISplatin, 5-Fluorouracil or to any of the excipients
- Known HER-2 positive GEJ carcinoma
- Information regarding prior therapy with an anti PD-1 or anti PD-L1 antibody is Available on NCCP website
- History of interstitial lung disease
- Pregnancy / breastfeeding
- Pre-existing renal impairment
- Significant hearing impairment / tinnitus
- Pre-existing neuropathies ≥ grade 2
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Blood glucose
- Thyroid function tests.
- Virology Screen: Hepatitis B (HBsAg, HbcoreAb) and Hepatitis C
- HER 2 testing of GEJ using a validated test method
- PD-L1 testing with the DAKO autostainer using the 22C3 Pharm DX antibody on the request of a Consultant Medical Oncologist where there is an intention to treat with pembrolizumab in line with this licensed indication
- Audiology and creatinine clearance if clinically indicated
- DPD testing prior to first treatment with 5-Fluorouracil 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 dihydropyrimidine dehydrogenase (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
- Blood glucose prior to each cycle
- Thyroid function tests every 6 weeks

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

Pembrolizumab dose modifications:

- Dose reduction is not recommended for pembrolizumab
- Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of pembrolizumab therapy and institution of systemic high-dose corticosteroid (see Table 5)

CISplatin and 5-Fluorouracil dose modifications:

- Dose reductions to manage chemotherapy induced adverse reactions are permitted for CISplatin and 5-Fluorouracil
- 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:

Table 3: Dose modification of CISplatin and 5-Fluorouracil for Haematological Toxicity

ANC (x 10^9/L		Platelets (x 10^9/L	Dose
≥ 1.5	and	≥ 100	100%
1 to < 1.5	or	75 to <100	**Delay**[a] then 100% for 1st event[b]
<1	or	<75	**Delay**[a] then 75%
[a]Delay until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L [b]Consider dose reduction to 75% for subsequent events and/ or prolonged delays of more than 2 weeks			

Renal and Hepatic Impairment:

Table 4: Recommended dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
Pembrolizumab[a]	No dose adjustment is needed Haemodialysis: no need for dose adjustment is expected		**Mild**	No dose adjustment is needed
			Moderate/Severe	No need for dose adjustment is expected
CISplatin[b]	50-59	75% of the original dose	No need for dose adjustment is expected	

	40-49	50% of the original dose				
	<40	Not recommended				
	Haemodialysis	50% of the original dose may be considered				
5-Fluorouracil[c]	No need for dose adjustment is expected Haemodialysis: no need for dose adjustment is expected		**Bilirubin**		**AST**	**Dose**
			<85		<180	100%
			>85	or	>180	Contra-indicated
			Clinical decision. Moderate hepatic impairment; reduce initial dose by 33%. Severe hepatic impairment, reduce initial dose by 50%. Increase dose if no toxicity.			

[a]Renal and hepatic dose recommendations from Giraud et al 2023
[b] Renal and hepatic dose recommendations from Giraud et al 2023
[c]Renal dose recommendations from Giraud et al 2023, hepatic dose recommendations from North London Cancer Network

Management of immune-related adverse events:

Table 5: Recommended treatment modifications for pembrolizumab

Immune-related adverse reactions	Severity (NCI-CTCAE v.4 grading)	Treatment modification
Pneumonitis	Grade 2	Withhold*
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue
Colitis	Grade 2 or 3	Withhold*
	Grade 4 or recurrent Grade 3	Permanently discontinue
Nephritis	Grade 2 with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN)	Withhold*
	Grade ≥ 3 with creatinine > 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 2 adrenal insufficiency and hypophysitis	Withhold treatment until controlled by hormone replacement
	Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis Type 1 diabetes associated with Grade ≥ 3 hyperglycaemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 3	Withhold* For patients with Grade 3 or Grade 4 endocrinopathy that improved to Grade 2 or lower and is controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise, treatment should be discontinued.
	Hypothyroidism	Hypothyroidism may be managed with replacement therapy without treatment interruption.

Hepatitis	Grade 2 with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN	Withhold*
	Grade ≥ 3 with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN	Permanently discontinue
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold*
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Other immune-related adverse reactions**	Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold*
	Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 3 or 4 Guillain-Barre syndrome Grade 4 or recurrent Grade 3	Permanently discontinue
Infusion-related reactions	Grade 3 or 4	Permanently discontinue

*Until adverse reactions recover to Grade 0-1. If treatment related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose of pembrolizumab or if corticosteroid dosing cannot be reduced to ≤ 10mg prednisone or equivalent per day within 12 weeks, pembrolizumab should be permanently discontinued
**Pembrolizumab should be permanently discontinued for Grade 4 or recurrent Grade 3 immune-related adverse reactions, unless otherwise specified in Table 5.

Management of adverse events:

Table 6: Dose modification schedule based on adverse events induced by CISplatin and 5-Fluorouracil

Adverse Event	Dose Modification
Stomatitis or Diarrhoea Grade 2 Grade ≥3	 Reduce dose of 5-Fluorouracil to 75% Discontinue or delay until toxicity resolved then resume at 50%.
Hand-foot syndrome Grade 2 Grade 3	Reduce dose of 5-Fluorouracil to 75% until resolved then consider increasing dose by 100% Delay until resolved then resume at 75%
Neurotoxicity Grade ≥ 2	 Omit CISplatin

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

Pembrolizumab: Minimal (**Refer to local policy)**
CISplatin: High (**Refer to local policy)**
5-Fluorouracil: Low **(Refer to local policy)**

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

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

- Pre and post hydration therapy required for CISplatin (**Refer to local policy** or see recommendations above)
- Anti-diarrhoeal treatment **(Refer to local policy).**
- Mouth care **(Refer to local policy).**

ADVERSE EFFECTS:

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

REGIMEN SPECIFIC COMPLICATIONS:

- **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 SmPC and drug interaction databases should be consulted for information.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

Patient Guide:
https://www.hpra.ie/img/uploaded/swedocuments/196f9071-00a4-4498-9dcb-e29ef7b35e55.pdf

Patient Alert Card:
https://www.hpra.ie/img/uploaded/swedocuments/c0984994-f8e8-4b10-95dd-7be12ff6c6f9.pdf

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Version	Date	Amendment	Approved By
1	01/06/2023		Prof Maccon Keane
1b	21/11/2023	Formatting changes and grammatical corrections.	NCCP
2	14/10/2024	Reviewed. Updated CISplatin pre hydration information. Updated exclusions section. Updated cautions section. Updated renal and hepatic dose modifications. Adverse Effects, regimen specific complications and Drug Interactions sections updated in line with NCCP standardisation.	Prof Maccon Keane
2a	03/03/2025	Additional wording added to baseline testing section.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] [i]EMA indication until 23/11/2023. HSE approved Reimbursement Status: ODMS from 01/06/2023. Centralised funding can be claimed by publicly funded hospitals via the ODMS.

To note the EMA license was amended on 23/11/2023

- *Pembrolizumab, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a CPS ≥ 10*
  - *(HSE approved Reimbursement Status: ODMS from 01/06/2023)*

- *Pembrolizumab, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1*
  - *HSE reimbursement assessment ongoing see here)*