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 is for 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. Prior therapy with an anti-PD-1 or anti-PD-L1 antibody is an exclusion criteria.

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.

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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 sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above.
Post hydration: Administer 1000 ml 0.9% NaCl over 60mins.

[4] Mannitol 10% may be used to 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.

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 sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above.
Post hydration: Administer 1000 ml 0.9% NaCl over 60mins.

[4] Mannitol 10% may be used to 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.

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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:

Use with caution in patients with:

- History of serious autoimmune disease

EXCLUSIONS:

- Hypersensitivity to pembrolizumab, CISplatin, 5-Fluorouracil or to any of the excipients
- Known HER-2 positive GEJ carcinoma
- Has received prior therapy with an anti-PD-1 or anti-PD-L1 antibody
- Active or unstable CNS metastases
- Any medical condition that requires immunosuppressive doses of systemic corticosteroids or other immunosuppressive medication(s) (defined as >10mg prednisolone/daily (or steroid equivalent, excluding inhaled or topical steroids)
- History of interstitial lung disease
- Any active clinically significant infection requiring therapy
- Pregnancy / breastfeeding
- Moderate / severe renal impairment (CrCl < 60 ml/min)
- Significant hearing impairment / tinnitus
- Pre-existing neuropathies ≥ grade 2
- Known complete dihydropyrimidine dehydroenase (DPD) deficiency where used in combination with 5-Fluorouracil

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Glucose
- Thyroid function tests.
- Virology Screen: Hepatitis B (HBsAg, HbcoreAb) and Hepatitis C

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- 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

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Glucose prior to each cycle
- Thyroid function tests every 3 to 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			

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Renal and Hepatic Impairment:

Table 4: Recommended dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
Pembrolizumab	**Mild/ Moderate**	No dose adjustment required	**Mild/Moderate**	No dose adjustment required
	Severe	Has not been studied	**Severe**	Has not been studied
CISplatin	**CrCl (ml/min)**	**Dose**	No dose modifications for hepatic impairment	
	≥60	100%		
	45-59	75%		
	<45	Consider CARBOplatin		
5-Fluorouracil	Consider dose reduction in severe renal impairment only		**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.	

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.

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	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

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SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

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 / 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.

Pembrolizumab

- **Immune-mediated adverse reactions:** Most immune-related adverse reactions occurring during treatment with pembrolizumab are reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of pembrolizumab. For suspected immune-related adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued over at least 1 month.
  Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Pembrolizumab may be restarted within 12 weeks after last dose of pembrolizumab if the adverse reaction remains at Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day. Pembrolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones. Specific guidelines for management of Immune Mediated Adverse Events are available.
- **Infusion-related reactions**: Severe infusion-related reactions have been reported in patients receiving pembrolizumab. For severe infusion reactions, infusion should be stopped and pembrolizumab permanently discontinued. Patients with mild or moderate infusion reaction may

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continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

CISplatin

- **Renal toxicity**: Nephrotoxicity is common with CISplatin. Strongly encourage oral hydration. If oral hydration is not possible (e.g. excessive nausea), IV hydration is indicated. Avoid nephrotoxic drugs such as aminoglycoside antibiotics where possible. Where treatment with nephrotoxic drugs must be used, monitor renal function.
- **Ototoxicity and sensory neural damage**: These are associated with CISplatin therapy. They should be assessed by history prior to each cycle.

5-Fluorouracil

- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with 5-Fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with5-Fluorouracil, should be carefully monitored during therapy.
- **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.
- **Hand-foot syndrome (HFS),** also known as palmar-plantar erythrodysaesthesia (PPE), has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-Fluorouracil.

DRUG INTERACTIONS:

- No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab. Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.
- The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided because of their potential interference with the pharmacodynamics activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions.
- Avoid concurrent use of CISplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of 5-Fluorouracil regimes.
- Concurrent administration of 5-Fluorouracil and phenytoin may result in increased serum levels of phenytoin.
- Caution should be taken when using 5-Fluorouracil in conjunction with medications which may affect DPD activity.
- Current drug interaction databases should be consulted for more information.

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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

REFERENCES:

1. Sun JM et al. KEYNOTE-590 Investigators. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet. 2021 Aug 28;398(10302):759-771. doi: 10.1016/S0140-6736(21)01234-4. Erratum in: Lancet. 2021 Nov 20;398(10314):1874. PMID: 34454674.
2. Metges J-P, Kato K, Sun J-M, Shah MA, Enzinger PC, Adenis A, et al. First-line pembrolizumab plus chemotherapy versus chemotherapy in advanced esophageal cancer: Longer-term efficacy, safety, and quality-of-life results from the phase 3 KEYNOTE-590 study. 2022;40(4_suppl):241-241.
3. Kato K et al. KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer. Future Oncol. 2019 Apr;15(10):1057-1066. doi: 10.2217/fon-2018-0609. Epub 2019 Feb 8. PMID: 30735435.
4. Irish Medication Safety Network: Best Practice Guidelines For the Safe Use of Intravenous Potassium in Irish Hospitals Available here.
5. Nephrotoxicity Associated with CISplatin EviQ ID: 184 v.3 https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/prophylaxis-andprevention/184-nephrotoxicity-associated-with-CISplatin 4
6. Portilla D et al. CISplatin nephrotoxicity. UptoDate available here https://www.uptodate.com/contents/CISplatinnephrotoxicity?source=search_result&search=CISplatin%20hydration&selectedTitle=1~150
7. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
8. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
9. 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
10. 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. 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
11. Pembrolizumab (Keytruda®) Summary of Product Characteristics. Last updated: 17/11/2022. Accessed May 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf

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12. CISplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics. Last updated 24/10/2022. Accessed May 2023. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-199-001_14032023145612.pdf
13. Fluorouracil 50mg/ml injection Summary of Product Characteristics. Last updated: 22/06/2022. Accessed May 2023. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-091-001_22062022113435.pdf

Version	Date	Amendment	Approved By
1	01/06/2023		Prof Maccon Keane
1b	21/11/2023	Formatting changes and grammatical corrections.	NCCP
1c	26/01/2024	Clarification of EMA MA update	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)*

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