Pembrolizumab Paediatric Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
As monotherapy for the treatment of paediatric patients aged 3 years and older with relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.	C81	P00711a	ODMS 01/02/2022
As monotherapy for the adjuvant treatment of adolescents aged 12 years and older with Stage IIB or IIC melanoma and who have undergone complete resection.	C43	P00711b	ODMS 01/12/2024

*This is for post 2012 indications only

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 is administered once every 21 days until disease progression or unacceptable toxicity.

For adjuvant melanoma therapy, the maximum treatment duration with pembrolizumab is 12 months.

Atypical responses (i.e. an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

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

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Pembrolizumab	2mg/kg (up to a maximum of 200mg)	IV infusion	50mL 0.9% NaCl over 30 minutes	Every 21 days
Pembrolizumab is diluted to a final concentration ranging from 1-10mg/mL.					
Administer using a low-protein binding 0.2 to 5 micrometre in-line or add-on filter.					

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

ELIGIBILITY:

- Indication as above
- Adequate haematological, hepatic and renal function
- **Classical Hodgkin lymphoma:**
  - ECOG status 0-1
- **Adjuvant melanoma:**
  - Confirmed new diagnosis of Stage IIB or IIC cutaneous melanoma per American Joint Committee (AJCC) on Cancer 8th edition guidelines

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- Adjuvant pembrolizumab should start within 12 weeks of surgery
- Performance status:
  - Patients >16 and <18 years: Karnofsky Performance Scale score ≥50
  - Patients ≤16 years: Lansky Play Performance Scale score ≥50

CAUTION:

- History of serious autoimmune disease

EXCLUSIONS:

- Known hypersensitivity to pembrolizumab or to any of the excipients
- Known clinically active central nervous system (CNS) involvement
- Active autoimmune disease that has required systemic treatment in the past 2 years
- Information regarding prior therapy with an anti PD-1 or anti PD-L1 antibody is Available on the NCCP website
- 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 and breastfeeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist or by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

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

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Glucose prior to each cycle
- Thyroid function tests every 3 to 6 weeks

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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.
- 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.
- Dose reduction is not recommended.
- Guidelines for withholding of doses or permanent discontinuation are described below in Table 1.

Table 1: 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

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	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 or4 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 1.

Renal and Hepatic Impairment:

Table 2: Dose modification of pembrolizumab in renal and hepatic impairment

Renal Impairment		**Hepatic Impairment**	
Mild/Moderate	No dose adjustment required	**Mild/Moderate**	No dose adjustment required
Severe	Has not been studied	**Severe**	Has not been studied
Renal and hepatic recommendations: Pembrolizumab SPC			

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

Minimal **(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) - Avaialble on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

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PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

- Women of childbearing potential should use effective contraception during treatment with pembrolizumab and for at least 4 months after the last dose of pembrolizumab.

ADVERSE EFFECTS

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

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/896369cd-ec45-4e3a-978f-bacea851002e.pdf

Patient Card
https://www.hpra.ie/img/uploaded/swedocuments/094590ae-1f3d-4b15-b76e-3b16bd642782.pdf

REFERENCES:

1. Geoerger B et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1-2 trial. Lancet Oncol. 2020 Jan; 21(1):121-133. doi: 10.1016/S1470-2045(19)30671-0. Epub 2019 Dec 4. PMID: 31812554.
2. Luke J et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double blind, phase 3 trial. Lancet 2022 Apr 30;399(10336):1718-1729
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. 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
4. Pembrolizumab (Keytruda®). Summary of Product Characteristics. Last updated: 17/11/2022. Accessed July 2024.Available at: https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf

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Version	Date	Amendment	Approved By
1	01/12/2023		Dr Jane Pears
2	13/08/2024	Regimen reviewed. New melanoma indication added. Renal and hepatic dose modifications updated in line with SPC. Regimen updated as per NCCP standardisation.	Prof Fergal Kelleher
2a	29/11/2024	Updated HSE reimbursement status for P00711b	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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