Pembrolizumab, PACLitaxel 175mg/m^2 and CARBOplatin AUC 5 Therapy

Note: There is an option for Pembrolizumab, PACLitaxel, CARBoplatin and Bevacizumab Therapy as described in NCCP regimen 00811

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1	C53	00817a	Pembrolizumab: Reimbursement by exception[i] PACLitaxel and CARBOplatin: hospital

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, PACLitaxel and CARBOplatin are administered on Day 1 of a 21 Day cycle and continued for 6 -8 cycles. Patients experiencing ongoing clinical benefit may continue beyond 6 cycles of PAClitaxel and CARBOplatin at the discretion of their treating clinician.

Pembrolizumab is continued as maintenance until disease progression or unacceptable toxicity occurs.

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 the systemic anti-cancer therapy (SACT) is administered.

Table 1. Pembrolizumab, PACLitaxel and CARBOplatin Therapy

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pembrolizumab[a]	200mg	IV infusion	100ml 0.9% NaCl over 30 mins using a low-protein binding 0.2 to 5 micrometre in-line or add-on filter	Every 21 days
2	1	PACLitaxel[b,c]	175mg/m^2	IV infusion	500ml 0.9% sodium chloride over 3 hours	Every 21 days
3	1	CARBOplatin	AUC 5	IV infusion	500ml glucose 5% over 30 mins	Every 21 days
[a]Pembrolizumab is diluted to a final concentration ranging from 1-10mg/ml.						
[b]PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22 µm filter with a microporous membrane.						
[c]PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.						

Table 2. Maintenance Therapy with Pembrolizumab

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Pembrolizumab[a]	200mg	IV infusion	100ml 0.9% NaCl over 30 mins using a low-protein binding 0.2 to 5 micrometre in-line or add-on filter	Every 21 days
[a]Pembrolizumab is diluted to a final concentration ranging from 1-10mg/ml.						

CARBOplatin dose:

The dose in mg of CARBOplatin to be administered is calculated as follows:

Dose (mg) = target AUC (mg/ml x min) x (GFR ml/min +25)

- **Measured GFR** (e.g. nuclear renogram) is preferred whenever feasible.
- **Estimation of GFR** may be performed using the Wright formula to estimate GFR or the Cockcroft and Gault formula to estimate creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- For obese patients and those with a low serum creatinine for example due to low body weight or post-operative asthenia, estimation using formulae may not give accurate results; measured GFR is recommended.
    - Where obesity (body mass index [BMI] ≥ 30 kg/m^2) or overweight (BMI 25-29.9) is likely to lead to an overestimate of GFR and isotope GFR is not available the use of the adjusted ideal body weight in the Cockcroft and Gault formula may be considered.
    - Where serum creatinine is less than 63 micromol/L, the use of a creatinine value of 62 micromol/L or a steady pre-operative creatinine value may be considered.
- These comments do not substitute for the clinical judgement of a physician experienced in prescription of CARBOplatin.

WRIGHT FORMULA

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. *SCr measured using enzymatic assay.*

$$\text{GFR (ml/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (micromol/min)}}$$

2. *SCr measured using Jaffe assay*

$$\text{GFR (ml/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \text{Sex})}{\text{SCr (micromol/min)}}$$

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

COCKCROFT-GAULT FORMULA

$$\text{GFR (ml/min)} = \frac{S \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

S= 1.04 for females

ELIGIBILITY:

- Indications as above
- ECOG Status 0-1
- Adequate haematological, hepatic and renal function

CAUTION:

- History of serious autoimmune disease
- Baseline neutrophil count < 1.5 x 10^9 cells/L

EXCLUSIONS:

- Hypersensitivity to pembrolizumab, PACLitaxel, CARBOplatin or any of the excipients
- Has received prior therapy with an anti-PD-1 or anti-PD-L1 antibody
- 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 or lactation
- Severe hepatic impairment (PACLitaxel)

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- PD-L1 expression using a validated test method
- Isotope GFR measurement (preferred) or GFR / Cr Clearance estimation
- Glucose
- Thyroid function tests
- Virology Screen: Hepatitis B (HBsAg, HBcoreAb) and Hepatitis C
- Audiometry if clinically indicated

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:

- 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 3).
- Any dose modification should be discussed with a Consultant.

Haematological:

Table 1: Dose modification of PACLitaxel and CARBOplatin in haematological toxicity

ANC (x 10^9/L) (pre-treatment blood test)	
≥1.0 to <1.5	Treatment should continue if patient is clinically well, Consultant decision
0.5 to 1.0	Delay treatment until recovery
< 0.5 and/ or febrile neutropenia	Delay treatment until recovery and consider reducing PACLitaxel and CARBOplatin by 25% for subsequent cycles
Platelets (x 10^9/L) (pre-treatment blood test)	
≥75 to <100	Treatment should continue if patient is clinically well, Consultant decision
50 to 75	Delay treatment until recovery
<50	Delay treatment until recovery and consider reducing PACLitaxel and CARBOplatin by 25% for subsequent cycles

Renal and Hepatic Impairment:

Table 2: Recommended dose modification for pembrolizumab, PACLitaxel and CARBOplatin in renal and hepatic impairment[a]

Drug	Renal Impairment		Hepatic Impairment			
Pembrolizumab	**Mild/Moderate**	No dose adjustment required	**Mild**			No dose adjustment required
	Severe	Has not been studied	**Moderate/Severe**			Has not been studied
CARBOplatin	See note below[b]		No dose modification required			
PACLitaxel	No dose modification required		ALT		Total bilirubin	Dose of PACLitaxel
			< 10 x ULN	and	≤ 1.25 x ULN	175mg/m^2
			< 10 x ULN	and	1.26-2 x ULN	135mg/m^2
			< 10 x ULN	and	2.01-5 x ULN	90mg/m^2
			≥ 10 x ULN	and/or	> 5 x ULN	Not recommended

[a]See Table 3 for management of pembrolizumab in treatment related hepatitis

[b]Renal dysfunction and CARBOplatin:

- Patients with creatinine clearance values of < 60ml/min are at greater risk of developing myelosuppression.
- If GFR between 20 to ≤ 30ml/min, CARBOplatin should be administered with extreme caution.
- In case of GFR ≤ 20ml/min CARBOplatin should not be administered at all.
- If Cockcroft & Gault or Wright formulas are used, the dose should be calculated as required per cycle based on a serum creatinine obtained within 48 hrs of drug administration.
- If isotope GFR is used, the dose should remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine is higher than this, consideration should be given to remeasuring the GFR or to estimating it using Cockcroft & Gault or Wright formulae.

Management of adverse events:

Table 3: 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	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 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 3.

Table 4: Recommended dose modification for PACLitaxel and CARBOplatin in adverse events

Adverse Reactions	Dose Modification
Peripheral Neuropathy	
Grade ≤ 2 which is present at the start of the next cycle	Reduce PACLitaxel by 25%; if persistent, reduce PACLitaxel by 50%
Grade ≥ 3	Omit PACLitaxel dose
Mucositis and stomatitis	
Grade 2 • 1st occurrence • 2nd occurrence • 3rd occurrence • 4th occurrence	Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: No dose reduction Reduce PACLitaxel and CARBOplatin by 25% Reduce PACLitaxel and CARBOplatin by 50% Omit PACLitaxel and CARBOplatin
Grade 3 or Grade 4 • 1st occurrence • 2nd occurrence	Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: Reduce PACLitaxel and CARBOplatin by 50% Omit PACLitaxel and CARBOplatin

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Pembrolizumab: Minimal **(Refer to local policy)**
CARBOplatin: High **(Refer to local policy)**
PACLitaxel: Low **(Refer to local policy)**

PREMEDICATIONS:

- All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to first dose of PACLitaxel treatment.
- The H_2 antagonist, famotidine, can potentially be omitted from the pre-medication requirements for PACLitaxel but the risk of hypersensitivity with this approach is unknown.
    - Caution is advised particularly for patients receiving PACLitaxel every 3 weeks. It is recommended that if famotidine is omitted that patients are monitored closely for any signs of hypersensitivity. Any hypersensitivity should be managed as per local policy.
    - Where a patient experiences hypersensitivity, consider the use of alternative H_2 antagonists **(Refer to local policy).**
- Table 5 outlines suggested premedications prior to treatment with PACLitaxel

Table 5: Suggested premedications prior to treatment with PACLitaxel

Drug	Dose	Administration prior to PACLitaxel
Dexamethasone	20mg oral or IV[a,b]	For oral administration: approximately 6 and 12 hours or for IV administration: 30 minutes
Chlorphenamine	10mg IV	30 minutes
Famotidine[c]	20mg IV	30 minutes
[a]Dose of dexamethasone may be reduced or omitted in the absence of hypersensitivity reaction according to		

consultant guidance.
[b]If aprepitant is added to the anti-emetic regimen, consideration should be given to reducing the dose of dexamethasone to 12mg on the day of treatment.
[c]Dose of famotidine may be omitted in the absence of hypersensitivity reaction according to consultant guidance.

OTHER SUPPORTIVE CARE:

- Myalgias and arthralgias may occur with PACLitaxel. Analgesic cover should be considered.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Pembrolizumab

- In view of the serious and potentially life-threatening side effects of pembrolizumab, it is mandatory that patients be carefully assessed prior to commencing on treatment. Efficacy and safety data from patients ≥ 75 years are limited. For patients ≥ 75 years, pembrolizumab combination therapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis Patients have to be monitored regularly for hepatic, pulmonary, gastrointestinal toxicity and for endocrinopathies while on treatment.
- **Immune-related adverse reactions:** Most immune-related adverse reactions occurring during treatment with pembrolizumab were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids or alternative immunosuppressants and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of pembrolizumab. Immune-related adverse reactions affecting more than one body system can occur simultaneously.
  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.
- **Immune-related pneumonitis**: Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 pneumonitis, and permanently discontinued for Grade 3, Grade 4 or recurrent Grade 2 pneumonitis.
- **Immune-related colitis:** Colitis has been reported in patients receiving pembrolizumab. Patients should be monitored for signs and symptoms of colitis, and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 or Grade 3 colitis, and

permanently discontinued for Grade 4 colitis. The potential risk of gastrointestinal perforation should be taken into consideration.

- **Immune-related hepatitis:** Hepatitis has been reported in patients receiving pembrolizumab. Patients should be monitored for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis, and other causes excluded. Corticosteroids should be administered (initial dose of 0.5-1 mg/kg/day (for Grade 2 events) and 1-2 mg/kg/day (for Grade ≥ 3 events) prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, pembrolizumab should be withheld or discontinued.
- **Immune-related nephritis**: Nephritis has been reported in patients receiving pembrolizumab. Patients should be monitored for changes in renal function, and other causes of renal dysfunction excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper) and, based on severity of creatinine elevations, pembrolizumab should be withheld for Grade 2, and permanently discontinued for Grade 3 or Grade 4 nephritis.
- **Immune-related endocrinopathies:** Severe endocrinopathies, including hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism, and hyperthyroidism have been observed with pembrolizumab treatment. Long-term hormone replacement therapy may be necessary in cases of immune-related endocrinopathies.

  Hypophysitis has been reported in patients receiving pembrolizumab. Patients should be monitored for signs and symptoms of hypophysitis (including hypopituitarism and secondary adrenal insufficiency) and other causes excluded. Corticosteroids to treat secondary adrenal insufficiency and other hormone replacement should be administered as clinically indicated, and pembrolizumab should be withheld for symptomatic hypophysitis until the event is controlled with hormone replacement. Continuation of pembrolizumab may be considered, after corticosteroid taper, if needed. Pituitary function and hormone levels should be monitored to ensure appropriate hormone replacement.

  Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving pembrolizumab. Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Insulin should be administered for type 1 diabetes, and pembrolizumab should be withheld in cases of Grade 3 hyperglycaemia until metabolic control is achieved. Thyroid disorders, including hypothyroidism, hyperthyroidism and thyroiditis, have been reported in patients receiving pembrolizumab and can occur at any time during treatment; therefore, patients should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically. Pembrolizumab should be withheld for Grade ≥ 3 until recovery to Grade ≤ 1 hyperthyroidism. For patients with Grade 3 or Grade 4 hyperthyroidism that improved to Grade 2 or lower, continuation of pembrolizumab may be considered, after corticosteroid taper, if needed. Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement.
- **Immune-related skin adverse reactions:** Immune-related severe skin reactions have been reported in patients receiving pembrolizumab. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. Based on the severity of the adverse reaction, pembrolizumab should be withheld or permanently discontinued, and corticosteroids should be administered. Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients receiving pembrolizumab). For signs or symptoms of SJS or TEN, pembrolizumab should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, pembrolizumab should be permanently

discontinued. Caution should be used when considering the use of pembrolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune stimulatory anticancer agents.

- **Other immune-related adverse reactions:** The following additional clinically significant, immune-related adverse reactions have been reported in patients receiving pembrolizumab: uveitis, arthritis, myositis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis and encephalitis. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. 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.**
- **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 continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

CARBOplatin

- **Hypersensitivity:** Reactions to CARBOplatin may develop in patients who have been previously exposed to platinum therapy. However allergic reactions have been observed upon initial exposure to CARBOplatin.
- **Neurotoxicity and ototoxicity.** Ototoxicity and sensory neural damage should be assessed by history prior to each cycle.
- **Renal toxicity:** The incidence and severity of nephrotoxicity may increase in patients who have impaired kidney function before CARBOplatin treatment.

PACLitaxel

- **Hypersensitivity:** Severe hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred in ≤1% of patients receiving PACLitaxel after adequate premedication. In the case of severe hypersensitivity reactions, PACLitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be re-challenged with the drug.
- **Extravasation:** PACLitaxel causes pain and tissue necrosis if extravasated. (Refer to local policy).
- **Neutropenia:** This is the dose limiting toxicity. Fever or other evidence of infection must be assessed promptly and treated appropriately. PACLitaxel should be administered when the neutrophil count is $> 1.5 \times 10^9$ cells/L.
- **Peripheral neuropathy:** Occurs frequently but the development of severe symptoms is rare. In severe cases, a dose reduction of 20% is recommended for all subsequent courses of PACLitaxel.
- **Arthralgia/myalgia:** May be severe in some patients; however, there is no consistent correlation between cumulative dose and infusion duration of PACLitaxel and frequency or severity of the arthralgia/myalgia. Symptoms are usually transient, occurring within 2 or 3 days after PACLitaxel administration, and resolving within days. Dose reducing PACLitaxel may lessen the severity of arthralgias/myalgias; however, there is no data on efficacy of reduced doses in a curative setting. Dose reduction should be considered only if symptom severity precludes continuing PACLitaxel.

- **Cardiac conduction abnormalities:** If patients develop significant conduction abnormalities during PACLitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with PACLitaxel. Hypotension, hypertension, and bradycardia have been observed during PACLitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of PACLitaxel infusion, is recommended.
- **Hepatic Dysfunction:** Patients with hepatic impairment may be at increased risk of toxicity, particularly grade 3-4 myelosuppression.

DRUG INTERACTIONS:

- The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided because of their potential interference with the pharmacodynamic 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 CARBOplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Avoid concurrent use of CARBOplatin with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS). When necessary perform regular audiometric testing.
- Risk of drug interactions causing increased concentrations of PACLitaxel with CYP3A inhibitors. Patients should also be counselled with regard to consumption of grapefruit juice.
- Risk of drug interactions causing decreased concentrations of PACLitaxel with CYP3A inducers.
- Current drug interaction databases should be consulted for more information.

COMPANY SUPPORT RESOURCES/Useful Links:

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

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

Pembrolizumab 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	17/04/2023		Prof Maccon Keane

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