Cemiplimab Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
As monotherapy for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy	C53	00812a	Reimbursement not approved[i]
As monotherapy is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (mCSCC or laCSCC) who are not candidates for curative surgery or curative radiation	C44	00812b	Reimbursement not approved[i]

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.

Cemiplimab is administered on day 1 of a 21 day cycle and continued until disease progression or unacceptable toxicity occurs.

Facilities to treat anaphylaxis MUST be present when the treatment is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Cemiplimab	350mg	IV infusion	[a]50ml NaCl 0.9% over 30 minutes	Every 21 days
Cemiplimab should be administered through an intravenous line containing a sterile, non-pyrogenic, low-protein binding, in-line or add-on filter (0.2 micron to 5 micron pore size). Other medicinal products should not be co-administered through the same infusion line.					
[a] Cemiplimab is diluted to a final concentration ranging from 1mg/ml to 20mg/ml					

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Adequate renal, hepatic and haematological function

EXCLUSIONS:

- Hypersensitivity to cemiplimab or any of the excipients
- 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)
- Any active clinically significant infection requiring therapy
- Has received prior therapy with an anti-PD-1 or anti-PD-L1 antibody
- Pregnancy/breastfeeding.

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

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Glucose prior to each cycle
- TSH 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:

- No dose reductions are recommended.
- Dosing delay or discontinuation may be required based on individual safety and tolerability.
- Recommended modifications to manage adverse reactions are provided in Table 1.

Renal and Hepatic Impairment:

Table 1: Dose modification in renal and hepatic impairment

Renal Impairment	**Hepatic Impairment**	
No dose adjustment is recommended for patients with renal impairment.	**Mild/moderate**	No dosage adjustment required
	Severe	Has not been studied

Management of adverse events:

Table 2: Dose Modification for Adverse Events

Adverse reactions	Severity[b]	Dose modification	Additional intervention
Immune-mediated reactions			
Pneumonitis	Grade 2	Withhold treatment	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume treatment if pneumonitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent	
	Grade 3 or 4 or recurrent grade 2	Permanently discontinue	Initial dose of 2 to 4 mg/kg/day prednisone or equivalent followed by a taper
Colitis	Grade 2 or 3	Withhold treatment	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume treatment if colitis or diarrhoea improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent	
	Grade 4 or recurrent Grade 3	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Hepatitis	Grade 2 with AST or ALT >3 and ≤ 5×ULN or total bilirubin > 1.5 and ≤ 3×ULN	Withhold treatment	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume treatment if hepatitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent or returns to baseline AST or ALT after completion of corticosteroid taper	
	Grade ≥ 3 with AST or ALT > 5×ULN or total bilirubin > 3×ULN	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Hypothyroidism	Grade 3 or 4	Withhold treatment	Initiate thyroid hormone replacement as clinically indicated
		Resume treatment when hypothyroidism returns to Grade 0 to 1 or is otherwise clinically stable	
Hyperthyroidism	Grade 3 or 4	Withhold treatment	Initiate symptomatic management
		Resume treatment when hyperthyroidism returns to Grade 0 to 1 or is otherwise clinically stable	
Thyroiditis	Grade 3 to 4	Withhold treatment	Initiate symptomatic management
		Resume treatment when thyroiditis returns to Grade 0 to 1 or is otherwise clinically stable	
Hypophysitis	Grade 2 to 4	Withhold treatment	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
		Resume treatment if hypophysitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent or is otherwise clinically stable	
Adrenal insufficiency	Grade 2 to 4	Withhold treatment	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
		Resume treatment if adrenal insufficiency improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or is otherwise clinically stable	
Type 1 diabetes	Grade 3 or 4	Withhold treatment	Initiate treatment with anti-hyperglycaemics

mellitus	(hyperglycaemia)		as clinically indicated
		Resume treatment when diabetes mellitus returns to Grade 0 to 1 or is otherwise clinically stable	
Skin adverse reactions	Grade 2 lasting longer than 1 week, Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold treatment	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume treatment if skin reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent	
	Grade 4 or confirmed SJS or TEN	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated skin reaction or other immune-mediated adverse reactions in patients with prior treatment with idelalisib	Grade 2	Withhold treatment	Initiate management immediately, including initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume treatment if skin reaction or other immune-mediated adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent	
	Grade 3 or 4 (excluding endocrinopathies) or recurrent Grade 2	Permanently discontinue	Initiate management immediately, including initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Nephritis with renal dysfunction	Grade 2 creatinine increased	Withhold treatment	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume treatment if nephritis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent	
	Grade 3 or 4 creatinine increased	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Other immune-mediated adverse reactions	Grade 2 or 3 based on type of reaction	Withhold treatment	Initiate symptomatic management including initial dose of 1 to 2 mg/kg/day prednisone or equivalent as clinically indicated followed by a taper
		Resume treatment if other immune-mediated adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent	
	-Grade 3 based on type of reaction or Grade 4(excluding endocrinopathies) –Grade 3 or 4 neurologic toxicity –Grade 3 or 4	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent as clinically indicated followed by a taper

	myocarditis or pericarditis –Recurrent Grade 3 immune-mediated adverse reaction –Persistent Grade 2 or 3 immune-mediated adverse reactions lasting 12 weeks or longer(excluding endocrinopathies) –Inability to reduce corticosteroid dose to10 mg or less of prednisone or equivalent per day within 12 weeks		
Infusion-related reactions			
Infusion-related reaction	Grade 1 or 2	Interrupt or slow rate of infusion	Initiate symptomatic management
	Grade 3 or 4	Permanently discontinue	
[b]Toxicity should be graded with the current version of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).			

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal (**Refer to local policy).**

PREMEDICATIONS: No specific recommendations

OTHER SUPPORTIVE CARE:

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

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

- **Immune-mediated adverse reactions:** Severe and fatal immune-mediated adverse reactions have been observed with cemiplimab. These immune-mediated reactions may involve any organ system. Immune-mediated reactions can manifest at any time during treatment with cemiplimab; however, immune-mediated adverse reactions can occur after discontinuation of cemiplimab. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously, such as myositis and myocarditis or myasthenia gravis, in patients treated with cemiplimab or other PD-1/PD-L1 inhibitors. Monitor patients for signs and symptoms of immune-mediated adverse reactions. Immune-mediated adverse reactions should be managed with cemiplimab treatment modifications, hormone replacement therapy (if clinically indicated), and corticosteroids. For suspected immune-mediated adverse reactions, patients should be evaluated to confirm an immune-mediated adverse reaction and to exclude other possible causes, including infection. Depending upon the severity of the adverse reaction, cemiplimab should be withheld or permanently discontinued
- **Infusion-related reactions:** Cemiplimab can cause severe or life-threatening infusion-related reactions. Patients should be monitored for signs and symptoms of infusion-related reactions and managed with cemiplimab treatment modifications and corticosteroids. Cemiplimab should be interrupted or the rate of infusion slowed for mild or moderate infusion-related reactions. The infusion should be stopped and cemiplimab should be permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions.
- **Pregnancy:** Cemiplimab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk.
- **Breast-feeding:** If a woman chooses to be treated with cemiplimab, she should be instructed not to breast-feed while being treated with cemiplimab and for at least 4 months after the last dose.

DRUG INTERACTIONS:

- No pharmacokinetic drug interaction studies have been conducted with cemiplimab.
- The use of systemic corticosteroids or immunosuppressants before starting cemiplimab, except for physiological doses of systemic corticosteroid (≤ 10 mg/day prednisone or equivalent), should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of cemiplimab. However, systemic corticosteroids or other immunosuppressants can be used after starting cemiplimab to treat immune-mediated adverse reactions.
- 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

Patient Alert Card: https://www.hpra.ie/img/uploaded/swedocuments/0a112454-53ed-400e-b236-c0d86d954701.pdf

Patient Guide: https://www.hpra.ie/img/uploaded/swedocuments/e8c3e05c-c726-4792-865c-768e86921c0c.pdf

REFERENCES:

1. Tewari TS, et al. Survival with Cemiplimab in Recurrent Cervical Cancer. N Engl J Med 2002;386:544-55.
2. Cemiplimab (Libtayo®) Summary of Product Characteristics. Accessed February 2023. Available at : https://www.ema.europa.eu/en/documents/product-information/libtayo-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	10/03/2023		Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] Post 2012 indication. Not reimbursed through the ODMS or Community Drug Schemes (including the High Tech arrangements of the PCRS community drug schemes). Please check https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/new.html for the most up to date reimbursement approvals.

ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes