CARBOplatin(AUC 2) Weekly and PACLitaxel (50mg/m^2) Weekly with Radiotherapy (RT) -5 weeks

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Preoperative chemoradiation treatment of oesophageal and gastro-oesophageal junction carcinomas	C15	00422a	Hospital

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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.

CARBOplatin and PACLitaxel are administered every **7 days,** concomitantly with radiotherapy for 5 weeks

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

Order of Admin	Day	Drug	Dose	Route and Method of Administration	Diluent & Rate
1	1,8,15,22 and 29	PACLitaxel	50mg/m^2	IV infusion	*250 ml 0.9% sodium chloride over 60 mins
2	1,8,15,22 and 29	CARBOplatin	AUC 2	IV infusion	250ml glucose 5% over 30 mins
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.					
*PACLitaxel should be diluted to a concentration of 0.3-1.2mg/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** (eGFR) 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.*

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

2. *SCr measured using Jaffe assay*

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

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 and 1.23 for males

ELIGIBILITY:

- Indications as above
- ECOG status 0-2
- Adequate haematological, renal, hepatic and pulmonary functions (ANC ≥ 1.5 x 10^9cells/L, platelets ≥ 100 x10^9/L, total bilirubin ≤1.5 x ULN, creatinine ≤ 120 micromol/L, FEV1 ≥1.5 L)

EXCLUSIONS:

- Hypersensitivity to CARBOplatin, PACLitaxel or any of the excipients
- Lactation
- Baseline neutrophil count <1.5x10^9 cells/L
- Severe hepatic impairment.

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Audiometry and creatinine clearance as clinically indicated
- Isotope GFR measurement (preferred) or GFR / Cr Clearance estimation

Regular tests:

- FBC, renal and liver profile before each cycle

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

Haematological:

Table 1: Recommended dose Modification in haematological toxicity

ANC (x 10^9/L) (on day of chemotherapy)		Platelets (x 10^9/L) (at any stage during cycle)	Dose Modification
≥1	and	≥50	100% Dose
<1	or	<50	Delay treatment for 1 week until recovery
Febrile neutropenia			Withhold further chemotherapy
Severe bleeding or requiring ≥ 2 platelet transfusions			

Renal and Hepatic Impairment:

Table 2: Recommended dose modification in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment	
CARBOplatin	See note below*	No dose modification required	
PACLitaxel	No dose modification required	Mild	75% dose
		Moderate	50% dose
		Severe	Discontinue

***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
- If GFR ≤ 20ml/min, CARBOplatin should not be administered at all
- If Cockcroft & Gault or Wright formula are used, the dose should be calculated as required on each cycle based on a serum creatinine obtained within 48 hrs of drug administration.
- If isotope GFR is used, the dose can remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine increases, consideration should be given to remeasuring the GFR or to estimating it using Cockcroft & Gault or Wright formulae, taking care this does result in a CARBOplatin dose reduction.

Management of adverse events:

Table 3: Recommended dose modification schedule based on adverse events

Adverse Reactions	Dose Modification
Peripheral Neuropathy Grade ≤ 2 Grade ≥ 3	 Continue Therapy Discontinue
Gastrointestinal Mucositis with oral ulcers or protracted vomiting despite antiemetic premedication.	Delay chemotherapy one week

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

CARBOplatin: Moderate **(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 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 4: Suggested pre-medications prior to treatment with PACLitaxel

Day of treatment	Drug	Dose	Administration prior to PACLitaxel
Day 1	Dexamethasone[a]	8mg IV	30 minutes
Day 1	Chlorphenamine	10mg IV	30 minutes
Day 1	Famotidine	20mg IV	30 minutes
Day 8[b] and thereafter	Dexamethasone[a]	None	
Day 8 and thereafter	Chlorphenamine	10mg IV	30 minutes
Day 8 and thereafter	Famotidine[c]	20mg IV	30 minutes
[a]Dose of dexamethasone may be altered, in the event of hypersensitivity reaction, to 20 mg of dexamethasone orally 12 hr and 6 hr prior to re-challenge with PACLitaxel according to consultant guidance.			
[b]Dose of dexamethasone may be added from day 8 if increased risk or previous hypersensitivity reaction according to consultant guidance.			
[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.

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:** Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose CARBOplatin. Neurotoxicity, such as parasthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with CISplatin, other platinum treatments and other ototoxic agents. Frequency of neurologic toxicity is also increased in patients older than 65 years.

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 x 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:

- 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 with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS). If 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.

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Version	Date	Amendment	Approved By
1	14/06/2017		Prof Maccon Keane
2	19/06/2019	Standardisation of volumes and diluents in the treatment table. Updated dose modification recommendations in haematological toxicity Standardisation of the pre-medication treatment table for PACLitaxel administration.	Prof Maccon Keane
3	23/06/2021	Reviewed. Updated CARBOplatin dosing section. Updated PACLitaxel pre meds table.	Prof Maccon Keane
4	29/08/2022	Updated CARBOplatin infusion time. Updated standard wording for CARBOplatin dosing and creatinine value. Updated dose modification of CARBOplatin in haematological toxicity. Updated PACLitaxel pre meds table. .	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.