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

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative chemoradiation treatment of oesophageal and gastro-oesophageal junction carcinomas</td>
<td>C15</td>
<td>00422a</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

*If the reimbursement status is not defined*, the indication has yet to be assessed through the formal HSE reimbursement process.

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 patient’s 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.

<table>
<thead>
<tr>
<th>Order of Admin</th>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route and Method of Administration</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1, 8, 15, 22 and 29</td>
<td>PACLitaxel</td>
<td>50mg/m^2</td>
<td>IV infusion</td>
<td>*250 ml 0.9% sodium chloride over 1 hr</td>
</tr>
<tr>
<td>2</td>
<td>1, 8, 15, 22 and 29</td>
<td>CARBOplatin</td>
<td>AUC 2</td>
<td>IV infusion</td>
<td>250ml glucose 5% over 60 min</td>
</tr>
</tbody>
</table>

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:

\[
\text{Dose (mg)} = \text{target AUC (mg/ml x min)} \times (\text{GFR ml/min} + 25)
\]

- Measured GFR (e.g. nuclear renogram) is preferred whenever feasible.
- Estimation of GFR (eGFR) can be done by using the Wright formula or using the Cockcroft and Gault formula to measure creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- For obese and anorexic patients the formulae may not give accurate results and measured GFR is recommended. Where obesity or overweight is likely to lead to an overestimate of GFR and isotope
GFR is not available the use of the adjusted ideal body weight for Cockcroft and Gault may be considered. (2)

**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.**

\[
GFR \ (\text{ml/min}) = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr} \ (\mu\text{mol/min})}
\]

2. **SCr measured using Jaffe assay**

\[
GFR \ (\text{ml/min}) = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \text{Sex})}{\text{SCr} \ (\mu\text{mol/min})}
\]

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

**COCKCROFT-GAULT FORMULA**

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

S= 1.04 for females and 1.23 for males

**ELIGIBILTY:**

- Indications as above
- ECOG status 0-2
- Adequate haematological, renal, hepatic and pulmonary functions (ANC ≥ 1.5 x 10^9 cells/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.

**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**

<table>
<thead>
<tr>
<th>ANC (x 10^9/L) (on day of chemotherapy)</th>
<th>Platelets (x 10^9/L) (at any stage during cycle)</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 and ≥50</td>
<td></td>
<td>100% Dose</td>
</tr>
<tr>
<td>&lt;1 or &lt;50</td>
<td></td>
<td>Delay treatment for 1 week until recovery</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td></td>
<td>Withhold further chemotherapy</td>
</tr>
<tr>
<td>Severe bleeding or requiring &gt;2 platelet transfusions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Renal and Hepatic Impairment:

Table 2: Recommended dose modification in renal and hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARBOplatin</td>
<td>See note below*</td>
<td>No dose modification required</td>
</tr>
<tr>
<td>PACLitaxel</td>
<td>No dose modification required</td>
<td>Mild 75% dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate 50% dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe Discontinue</td>
</tr>
</tbody>
</table>

*Renal dysfunction and CARBOplatin:

- Patients with creatinine clearance values of <60ml/min are at greater risk to develop myelosuppression.
- In case of GFR ≤ 20ml/min CARBOplatin should not be administered at all.
- If Cockroft & Gault or Wright formula is used, the dose should be adjusted 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 recalculating using Cockroft & Gault or Wright formulae taking care this does result in a dose reduction.

Management of adverse events:

Table 3: Recommended dose modification schedule based on adverse events

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral Neuropathy</strong></td>
<td></td>
</tr>
<tr>
<td>Grade ≤ 2</td>
<td>Continue Therapy</td>
</tr>
<tr>
<td>Grade ≥ 3</td>
<td>Discontinue</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Mucositis with oral ulcers or protracted vomiting despite antiemetic premedication</td>
<td>Delay chemotherapy one week</td>
</tr>
</tbody>
</table>

**SUPPORTIVE CARE:**

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

**PREMEDICATIONS:**

All patients must be premedicated with corticosteroids, antihistamines, and H₂ antagonists prior to PACLitaxel treatment. Table 4 outlines suggested pre-medications prior to treatment with PACLitaxel

Table 4: Suggested pre-medications prior to treatment with PACLitaxel

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Administration prior to PACLitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>10mg IV</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Chlorphenamine</td>
<td>10mg IV</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>50mg IV</td>
<td>30 minutes</td>
</tr>
</tbody>
</table>

*Dose of dexamethasone may be reduced or omitted in the absence of hypersensitivity reaction according to consultant guidance.

*The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient’s care or treatment. Use of these documents is the responsibility of the prescribing clinician. and is subject to HSE’s terms of use available at [http://www.hse.ie/eng/Disclaimer](http://www.hse.ie/eng/Disclaimer)*
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 paraesthesia, 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 10⁹ 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

### Table

<table>
<thead>
<tr>
<th>NCCP Protocol: CARBOplatin (AUC2), PACLitaxel 50mg/m² Plus RT-21 day</th>
<th>Published: 07/07/2017</th>
<th>Version number: 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour Group: Gastrointestinal TCCP Protocol Code: 00422</td>
<td>Review: 19/06/2021</td>
<td>ISMO Contributor: Prof Maccon Keane</td>
</tr>
<tr>
<td>Page 5 of 6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.

**ATC CODE:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>ATC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARBOplatin</td>
<td>L01XA02</td>
</tr>
<tr>
<td>PACLitaxel</td>
<td>L01CD01</td>
</tr>
</tbody>
</table>

**REFERENCES:**


<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14/06/2017</td>
<td>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.</td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>2</td>
<td>19/06/2019</td>
<td>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.</td>
<td>Prof Maccon Keane</td>
</tr>
</tbody>
</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

---

1 ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at; [http://www.hse.ie/eng/services/list/5/cancer/proinfo/medonc/cdmp/](http://www.hse.ie/eng/services/list/5/cancer/proinfo/medonc/cdmp/)

NCCP Protocol: CARBOplatin(AUC2), PACLitaxel 50mg/m² Plus RT-21 day
Published: 07/07/2017
Review: 19/06/2021
Version number: 2
Tumour Group: Gastrointestinal
NCCP Protocol Code: 00422
ISM0 Contributor: Prof Maccon Keane
Page 6 of 6

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician. and is subject to HSE’s terms of use available at [http://www.hse.ie/eng/Disclaimer](http://www.hse.ie/eng/Disclaimer)

This information is valid only on the day of printing, for any updates please check [www.hse.ie/NCCPchemoprotocols](http://www.hse.ie/NCCPchemoprotocols)