

Weekly CARBOplatin (AUC2) PACLitaxel 50mg/m² Therapy with Radiotherapy

INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | Reimbursement Status |
|--|-------|--------------|----------------------|
| Stage III Non small cell lung cancer (NSCLC) | C34 | 00309a | 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.

Adjuvant treatment:

CARBOplatin and PACLitaxel are administered once a week for 7 weeks with concurrent radiotherapy or until disease progression or unacceptable toxicity develops.

Consolidation chemotherapy with CARBOplatin (AUC6) and PACLitaxel 200mg/m² Therapy (Reference NCCP regimen 00304) for 2 cycles may start after completion of concurrent radiotherapy.

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

| Admin. Order | Day | Drug | Dose | Route | Diluent & Rate | Cycle |
|---|-----|-------------|----------------------------------|-------------|-------------------------------|--------------------------|
| 1 | 1 | PACLitaxel | ^a 50mg/m ² | IV infusion | 250ml 0.9% NaCl over 60min | Every 7 days for 7 weeks |
| 2 | 1 | CARBOplatin | AUC 2 | IV infusion | 250mls glucose 5% over 60 min | Every 7 days for 7 weeks |
| ^a A lower dose of 45mg/m ² PACLitaxel may be administered at the discretion of the prescribing Consultant | | | | | | |
| 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 (4).

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| NCCP Regimen: Weekly CARBOplatin (AUC 2) and Weekly PACLitaxel 50mg/m ² Therapy | Published: 08/04/2016 Review: 29/04/2025 | Version number: 4 |
| Tumour Group: Lung NCCP Regimen Code: 00309 | ISMO Contributor: Prof Maccon Keane | Page 1 of 6 |
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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 and 1.23 for males

ELIGIBILITY:

- Indications as above
- Life expectancy > 3months
- ECOG status 0-2
- Patients unsuitable for CISplatin therapy due to co-morbidities, poor renal function
- Adequate organ function; ANC > 1.5 x10⁹ cells/L, platelets ≥ 100 x10⁹/L

EXCLUSIONS:

- Hypersensitivity to CARBOplatin*, PACLitaxel or any of the excipients.
- Pregnancy or lactation
- Severe hepatic impairment (PACLitaxel)
- Baseline neutrophil count < 1.5 x 10⁹ cells/L
- Significant pleural effusions

PRESCRIPTIVE AUTHORITY:

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

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TESTS:

Baseline tests:

- FBC, renal and liver profile
- Audiometry and creatinine clearance as clinically indicated

Regular tests:

- FBC with differential, renal and liver profile weekly during treatment
- Assessment of peripheral neuropathy status as clinically indicated

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: Dose modifications for haematological toxicity on treatment days

| ANC (x 10 ⁹ /L) | | Platelet count (x 10 ⁹ /L) | Dose |
|----------------------------|--------|---------------------------------------|--|
| ≥ 1 | and | >50 | 100% Dose |
| < 1 | and/or | <50 | Delay chemotherapy for 1 week until recover above these values |

Renal and hepatic impairment

Table 2: Dose Modification of CARBOplatin and PACLitaxel in renal and hepatic impairment

| Drug | Renal Impairment | Hepatic Impairment |
|--------------------|-------------------------------|---|
| CARBOplatin | See note below ^b | No dose modification required |
| PACLitaxel | No dose modification required | For mild and moderate impairment discuss with Consultant. Not recommended in severe hepatic impairment |

^bRenal 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 Cockcroft & Gault or Wright formula are 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 Cockcroft & Gault or Wright formulae taking care this does result in a dose reduction.

Management of adverse events:

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Peripheral Neuropathy:

Dose modification or discontinuation may be required. Discuss with consultant.

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 3 outlines suggested premedications prior to treatment with PACLitaxel.

Table 3: Suggested premedications prior to treatment with PACLitaxel

| Drug | Dose | Administration prior to PACLitaxel |
|--|------------------------|------------------------------------|
| Dexamethasone | 10mg IV ^{a,b} | 30 minutes |
| Chlorphenamine | 10mg IV | 30 minutes |
| RaNITidine ^c | 50mg IV | 30 minutes |
| ^a Dose of dexamethasone may be reduced or omitted in the absence of hypersensitivity reaction according to consultant guidance. | | |
| ^b Dose of dexamethasone may be altered in the event of hypersensitivity reaction to 20 mg of dexamethasone orally 12 and 6 hr prior to re-challenge with PACLitaxel according to consultant guidance. | | |
| ^c or equivalent e.g. Cimetidine | | |

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.

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **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.
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.
- **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.

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- **Peripheral neuropathy:** Occurs frequently but the development of severe symptoms is rare. Dose reduction or discontinuation may be necessary.
- **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.
- **Hepatic Dysfunction:** Patients with hepatic impairment may be at increased risk of toxicity, particularly grade 3-4 myelosuppression.
- **Extravasation:** PACLitaxel causes pain and tissue necrosis if extravasated. **(Refer to local policy).**
- **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.

DRUG INTERACTIONS:

- Avoid concurrent use 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). When necessary perform regular audiometric testing
- Risk of drug interactions causing increased concentrations of PACLitaxel with CYP3A inhibitors.
- Risk of drug interactions causing decreased concentrations of PACLitaxel with CYP3A inducers.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

CARBOplatin L01XA02
 PACLitaxel L01CD01

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| Version | Date | Amendment | Approved By |
|---------|------------|--|-------------------|
| 1 | 08/04/2016 | | Prof Maccon Keane |
| 2 | 18/04/2018 | Updated with new NCCP regimen template. Title and Treatment table updated for standardisation. Updated dosing in haematological toxicity | Prof Maccon Keane |
| 3 | 23/10/2019 | Standardised table for suggested premedications prior to treatment with PACLitaxel | Prof Maccon Keane |
| 4 | 29/04/2020 | Exclusion criteria updated Updated references | Prof Maccon Keane |

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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