CARBOplatin AUC 5 and Pegylated Liposomal DOXOrubicin 30mg/m^2 Therapy-28 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of patients with platinum sensitive relapsed/ recurrent			Hospital
• ovarian	C56	00624a	
• primary peritoneal	C57	00624b	
• fallopian tube cancer	C48	00624c	

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 Pegylated Liposomal DOXOrubicin are both administered on day 1 of a 28 day cycle for 6 cycles or until disease progression or unacceptable toxicity occurs. Additional cycles are allowed for patients experiencing response or stable disease.

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

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	**1**	Pegylated Liposomal DOXOrubicin (Caelyx®)	30mg/m^2	IV infusion	[a]250ml glucose 5% at rate of 1mg/min for first cycle (see note)	28 days
2	1	CARBOplatin	AUC 5	IV infusion	500ml glucose 5% over 60 min	28 days

[a]For doses ≥ 90mg, use 500mL infusion bag
Do not use with in-line filters

NOTE: If no infusion reaction observed subsequent infusions may be administered over 60min.

For patients who experience an infusion reaction, the method of infusion should be modified as follows: 5% of the total dose should be infused slowly over the first 15 minutes. If tolerated without reaction, the infusion rate may then be doubled for the next 15 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes.

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)** can be done by using the Wright formula or using the Cockroft 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 Cockroft 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*.

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

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

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

S= 1.04 for females and 1.23 for males

ELIGIBILITY:

- Indications as above
- Histologically confirmed diagnosis of cancer of the ovary, fallopian tube or extraovarian papillary serous tumour
- Disease progression longer than 6 months after first or second line platinum-based chemotherapy regimen
- ECOG 0-2
- Adequate haematologic, renal and hepatic and cardiac function

EXCLUSIONS:

- Hypersensitivity to CARBOplatin, pegylated liposomal DOXOrubicin, peanut, soya or to any of the excipients
- Pre-existing neuropathy grade >1
- Pre-existing cardiac myopathy or congestive heart failure
- Hepatic dysfunction (see Dose Modifications below)
- Pregnancy or lactation

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- ECG
- MUGA or ECHO (to determine LVEF)

Regular tests:

- FBC, renal and liver profile prior to each cycle
- ECG
- *MUGA or ECHO (to determine LVEF as clinically indicated)
  *See Adverse Effects/Regimen specific complications for guidelines regarding cardiotoxicity

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 modification levels for pegylated liposomal DOXOrubicin (CAELYX) and CARBOplatin in haematological toxicity

Drug	Dose level 0	Dose level -1
pegylated liposomal DOXOrubicin	30mg/m^2	25mg/m^2
CARBOplatin	AUC 5	AUC 4

Table 2: Specific dose modifications for pegylated liposomal DOXOrubicin (CAELYX) and CARBOplatin in haematological toxicity

Adverse event	Dose modification
Grade 4 neutropenia (ANC <1.0 x 10^9/L)	Reduce dose of both drugs by one level
Febrile neutropenia or severe bleeding	Reduce dose of both drugs by one level
Prolonged neutropenia and thrombocytopenia	Dose delay until full recovery (up to 14 days)
Dose re-escalation is not allowed after a required dose reduction. If recovery was not sufficient despite adequate countermeasures and/or course delays after a dose reduction to level −1 of pegylated liposomal DOXOrubicin, treatment with peglylated liposomal DOXOrubicin is discontinued and the patient is treated with CARBOplatin alone	

Renal and Hepatic Impairment:

Table 3: Dose modification of pegylated liposomal DOXOrubicin (CAELYX) and CARBOplatin in renal and hepatic impairment

<table>
<tr><th>Drug</th><th>Renal Impairment</th><th colspan="2">Hepatic Impairment</th></tr>
<tr><td rowspan="3">pegylated liposomal DOXOrubicin</td><td rowspan="3">No dose reduction necessary</td><td>Bilirubin (micromol/L)</td><td>Dose</td></tr>
<tr><td>20-51</td><td>75%</td></tr>
<tr><td>>51</td><td>50%</td></tr>
<tr><td colspan="3">If the patient tolerates the first dose without an increase in serum bilirubin or liver enzymes, the dose for cycle 2 can be increased to the next dose level, i.e., if reduced by 25 % for the first dose, increase to full dose for cycle 2; if reduced by 50 % for the first dose, increase to 75 % of full dose for cycle 2. The dosage can be increased to full dose for subsequent cycles if tolerated. Pegylated liposomal DOXOrubicin can be administered to patients with liver metastases with concurrent elevation of bilirubin and liver enzymes up to 4 x the upper limit of the normal range.</td></tr>
<tr><td>CARBOplatin</td><td>• 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 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 Cockroft & Gault or Wright formulae taking care this does result in a dose reduction</td><td colspan="2">No dose modification required</td></tr>
</table>

Management of adverse events:

Table 4: Dose Modification of pegylated liposomal DOXOrubicin (CAELYX) in Palmar-Plantar Erythrodysesthesia (PPE) and Stomatitis

Week after prior pegylated liposomal DOXOrubicin dose			
Toxicity Grade At Current Assessment	**Week 4**	**Week 5**	**Week 6**
Grade 1	**Redose unless** patient has experienced a previous Grade 3 or 4 skin toxicity or stomatitis, in which case wait an additional week	**Redose unless** patient has experienced a previous Grade 3 or 4 skin toxicity or stomatitis, in which case wait an additional week	PPE and stomatitis: Decrease dose by 25 %; OR Stomatitis: Consider discontinuation - clinician decision
Grade 2	Wait an additional week	Wait an additional week	PPE and stomatitis: Decrease dose by 25 %; OR Stomatitis: Consider discontinuation - clinician decision
Grade 3	Wait an additional week	Wait an additional week	Discontinue
Grade 4	Wait an additional week	Wait an additional week	Discontinue

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

pegylated liposomal DOXOrubicin - Low (**Refer to local policy).**
CARBOplatin **–** High (**Refer to local policy).**

PREMEDICATIONS: None usually required

OTHER SUPPORTIVE CARE:

- Other strategies to prevent and treat PPE, which may be initiated for 4 to 7 days after treatment with pegylated liposomal DOXOrubicin include keeping hands and feet cool, by exposing them to cool water (soaks, baths, or swimming), avoiding excessive heat/hot water and keeping them unrestricted (no socks, gloves, or shoes that are tight fitting) (**Refer to local policy**).
- Primary prophylaxis with G-CSF should be considered to reduce the risk of neutropenic complications **(Refer to local policy)**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

Pegylated liposomal DOXOrubicin:

- **Cardiotoxicity**: Frequent ECG monitoring is recommended. Reduction of the QRS complex suggests cardiac toxicity. LVEF monitoring using ECHO or MUGA should be applied during treatment. The evaluation of LVEF is considered to be mandatory before each additional administration of pegylated liposomal DOXOrubicin that exceeds a lifetime cumulative anthracycline dose of 450 mg/m^2. Cardiac toxicity also may occur at cumulative anthracycline doses lower than 450 mg/m^2 in patients with prior mediastinal irradiation or in those receiving concurrent cyclophosphamide therapy.
- **Acute Infusion Reaction:** Usually seen during the first infusion. For patients who experience an infusion reaction, the method of infusion should be modified as follows: 5% of the total dose should be infused slowly over the first 15 minutes. If tolerated without reaction, the infusion rate may then be doubled for the next 15 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes.
- **Palmar-plantar erythrodysesthesia syndrome (PPE**): Monitor patient for presence of PPE. If present, patient may require an interruption in treatment (see dose modifications).
- **Extravasation**: Pegylated liposomal DOXOrubicin is considered an irritant**. (Refer to local guidelines).**

CARBOplatin:

- **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.
- **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

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information.

Pegylated liposomal DOXOrubicin:

- No formal medicinal product interaction studies have been carried out.
- Exercise caution in the concomitant use of pegylated liposomal DOXOrubicin with products known to interact with standard DOXOrubicin hydrochloride

CARBOplatin:

- 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). If necessary perform regular audiometric testing.

ATC CODE:

DOXOrubicin - L01DB01
CARBOplatin - L01XA02

REFERENCES:

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Version	Date	Amendment	Approved By
1	18/12/2020		Prof Maccon Keane

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