# Bevacizumab 10mg/kg and Pegylated Liposomal DOXOrubicin 40mg/m$^2$ Therapy

**Please note that the Myocet® product, which contains non-pegylated liposomal DOXOrubicin should not be used when treating patients with this regimen.**

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | HSE approved reimbursement status* |
|---|---|---|---|
| For the treatment of adult patients with platinum-resistant recurrent epithelial ovarian,<br>fallopian tube, or<br>primary peritoneal cancer<br>who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents. | C56<br>C57<br>C48 | 00772a | N/A |

*This is for post 2012 indications only

## 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.*

Bevacizumab is administered on Days 1 and 15 and pegylated liposomal DOXOrubicin is administered on Day 1 of a 28 day cycle until disease progression or unacceptable toxicity occurs.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

| Day | Drug | Dose | Route | Diluent & Rate | Cycle |
|---|---|---|---|---|---|
| 1, 15 | Bevacizumab | 10mg/kg | IV infusion | 100mL NaCl 0.9% over 90 minutes[a] | Every 28 days |
| 1 | Pegylated liposomal DOXOrubicin[b] | 40mg/m$^2$ | IV infusion | 250mL[c] glucose 5% at rate of 1mg/minute for first cycle (see note) | Every 28 days |

[a] The initial dose of bevacizumab should be delivered over 90 minutes as an intravenous infusion.

If the first infusion is well tolerated, the second infusion may be administered over 60 minutes.

If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

Alternatively, the unlicensed use of shorter infusion times is described in the NCCP Bevacizumab Rapid Infusion Rate Guidance here [i]

It should not be administered as an intravenous push or bolus.

Flush line with NaCl 0.9% pre and post bevacizumab dose as it should not be mixed with glucose solutions.

[b] Lifetime cumulative dose of doxorubicin is 450mg/m$^2$ In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below[i] and to the age of the patient.

[c] 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 60 minutes.
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.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

## ELIGIBILITY:

- Indication as above
- ECOG status 0-2
- Adequate organ function

## EXCLUSIONS:

- Hypersensitivity to bevacizumab, pegylated liposomal DOXOrubicin or to any of the excipients
- Baseline neutrophil count < $1.5x10^9$ cells/L
- Pregnancy
- Breastfeeding
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies
- Pre-existing cardiac myopathy or congestive heart failure
- Hepatic dysfunction (see Dose Modifications below)

## USE WITH CAUTION:

Use with caution in patients with:

- Previous pelvic radiotherapy
- Pre-existing uncontrolled hypertension
- Clinically significant cardiovascular disease
- Renal disease including proteinuria
- Bleeding/Clotting disorders
- Previous anthracycline exposure
- History of significant venous thromboembolism
- Recent (less than 6 months) arterial thromboembolic events
- Prior radiation to the chest wall or other serious medical illness
- Surgical procedure or complications that could lead to increased risk of fistulation or perforation
- Underlying condition that could lead to increased risk of fistulation or perforation

## PRESCRIPTIVE AUTHORITY:

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

## TESTS:

**Baseline tests:**

- FBC, renal and liver profile
- Dipstick urinalysis for protein
- Blood pressure measurement, cardiac assessment including history and physical exam
- MUGA, ECHO (LVEF > 50% to administer DOXOrubicin) if >65 years
- ECG

INR if clinically indicated*
*(For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle.)

**Regular tests:**

- FBC, renal and liver profile
- Blood pressure prior to each cycle and post treatment
- INR if clinically indicated*
- MUGA, ECHO as clinically indicated

*(For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to 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

- Bevacizumab dose reduction for adverse events is not recommended (SmPC). If indicated, bevacizumab therapy should either be permanently discontinued or temporarily suspended until toxicity resolves (Table 4 and Table 5).
- Dose reductions for pegylated liposomal DOXOrubicin are outlined below.

## Haematological:

**Table 1: Recommended dose modification of pegylated liposomal DOXOrubicin for haematological toxicity**

| ANC ($x10^9$/L) | | Platelets ($x10^9$/L) | Dose |
|---|---|---|---|
| 1.5-1.9 | and | ≥75 | **100%** |
| 1-<1.5 | or | 50-74 | Wait until ANC ≥ 1.5 and platelets ≥ 75; redose with no dose reduction. |
| 0.5-<1 | or | <50 | Wait until ANC ≥ 1.5 and platelets ≥ 75; redose with no dose reduction. |
| <0.5 | or | <25 | Wait until ANC ≥ 1.5 and platelets ≥ 75; decrease dose by 25% or continue full dose with growth factor support. |

## Renal and Hepatic Impairment:

**Table 2: Recommended dose modification for bevacizumab and pegylated liposomal DOXOrubicin in renal and hepatic impairment**

<table>
<tr><th>Drug</th><th>Renal Impairment</th><th colspan="2">Hepatic Impairment</th></tr>
<tr><td>Bevacizumab [a]</td><td>No need for dose adjustment is expected<br><br>Haemodialysis: no need for dose adjustment is expected</td><td colspan="2">No need for dose adjustment is expected</td></tr>
<tr><td colspan="2" rowspan="2">Pegylated liposomal DOXOrubicin [b]<br><br>No need for dose adjustment is expected</td><td>Bilirubin (micromol/L)</td><td>Dose</td></tr>
<tr><td>20-50</td><td>75% of the original dose</td></tr>
</table>

| | | |
|---|---|---|
| Haemodialysis: no need for dose adjustment is expected | >51-86 | 50% of the original dose |
| | >86 | Not recommended |

[a] Bevacizumab (renal and hepatic - Giraud et al 2023);

[b] Pegylated liposomal DOXOrubicin (renal and hepatic – Giraud et al 2023)

## Management of adverse events:

**Table 3: Dose Modification of pegylated liposomal DOXOrubicin for Palmar-Plantar Erythrodysesthesia (PPE) and Stomatitis**

| Week after prior pegylated liposomal DOXOrubicin dose | | | |
|---|---|---|---|
| **Toxicity Grade At Current Assessment** | **Day 1 of new cycle** | **Delayed one week** | **Delayed 2 weeks** |
| **Grade 1** | **Proceed with dose unless** patient has experienced a previous Grade 3 or 4 skin toxicity or stomatitis, in which case delay 1 week | **Proceed with dose unless** patient has experienced a previous Grade 3 or 4 skin toxicity or stomatitis, in which case delay another week | PPE and stomatitis: Decrease dose by 25%;<br>OR<br>Stomatitis: Consider discontinuation - clinician decision |
| **Grade 2** | Delay 1 week | Delay an additional week | PPE and stomatitis: Decrease dose by 25%;<br>OR<br>Stomatitis: Consider discontinuation - clinician decision |
| **Grade 3** | Delay 1 week | Delay an additional week | Discontinue |
| **Grade 4** | Delay 1 week | Delay an additional week | Discontinue |

## Proteinuria:

**Table 4: Dose modifications of bevacizumab for proteinuria**

| **Degree of proteinuria** | **Action** |
|---|---|
| Neg or 1+ dipstick or less than 1 g/L laboratory urinalysis for protein | Administer bevacizumab dose as scheduled |
| 2+ or 3+ dipstick or greater than or equal to 1 g/L laboratory urinalysis for protein | Administer bevacizumab dose as scheduled. Collect 24-hour urine for determination of total protein within 3 days before the next scheduled bevacizumab administration. Adjust bevacizumab treatment based on the table below |
| If urine dipstick shows 4+ at baseline or during treatment | Withhold bevacizumab and proceed with 24 hour urine collection. |
| **24-hour urine total protein (g/24hr)** | **Action** |
| less than or equal to 2 | Proceed |
| greater than 2 to 4 | Hold dose and recheck 24 hour urine every 2 weeks, resume therapy when less than or equal to 2g/24hour |
| greater than 4 | Discontinue Therapy |

**Table 5: Dose modifications of bevacizumab for adverse events**

| Adverse reactions | | Recommended dose modification |
|---|---|---|
| **Hypertension** | Uncontrolled * or symptomatic hypertension on Day 1 | Withhold bevacizumab treatment and start antihypertensive therapy or adjust pre-existing medication |
| | Grade 2-3 hypertension | Initiate antihypertensive therapy and consider interruption of bevacizumab until controlled |
| | Grade 4 hypertension or persisting grade 3 hypertension | Discontinue bevacizumab |
| **Grade 4 Proteinuria** | | Discontinue bevacizumab |

| | |
|---|---|
| **Tracheoesophageal (TE) fistula or any Grade 4 fistula** | Discontinue bevacizumab |
| **Grade 4 Thromboembolic events** | Discontinue bevacizumab |
| **Haemorrhagic event ≥ Grade 3** | Discontinue bevacizumab |
| **Gastrointestinal Perforation** | Discontinue bevacizumab |
| *Uncontrolled hypertension for initiating bevacizumab is defined as sustained BP>150/100mmHg while receiving anti-hypertensive medication | |

## SUPPORTIVE CARE:

### EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting Available on the NCCP website

Bevacizumab: Minimal **(Refer to local policy).**
Pegylated liposomal DOXOrubicin: Low **(Refer to local policy).**

**For information:**

**Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:**

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

**PREMEDICATIONS:** Not usually required unless the patient has had a previous hypersensitivity.

### OTHER SUPPORTIVE CARE:

Anti-diarrhoeal treatment may be required **(Refer to local policy).**

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**).

## ADVERSE EFFECTS

Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

## DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

## REFERENCES:


1. Pujade-Lauraine,E, Hilpert, F et al. Bevacizumab Combined With Chemotherapy for Platinum-Resistant Recurrent Ovarian Cancer: The AURELIA Open- Label Randomized Phase III Trial. J Clin Oncol. 2014; 32:(13) 1302-1308.
2. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
4. Bevacizumab (Avastin®) Summary of product characteristics EMA. Last updated 17/03/2023. Accessed March 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf
5. Pegylated liposomal DOXOrubicin (CAELYX®) Summary of Product Characteristics. Last updated 05/09/2023. Accessed March 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/caelyx-pegylated-liposomal-epar-product-information_en.pdf


| Version | Date | Amendment | Approved By |
|---|---|---|---|
| 1 | 14/11/2022 | | Prof. Maccon Keane |
| 2 | 28/07/2023 | Removal of brand name. Updated dose modification table for bevacizumab. | Prof. Maccon Keane |
| 3 | 05/07/2024 | Reviewed.Updated treatment table in line with NCCP | Prof. Maccon Keane |

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|---|---|---|---|
| | | standardisation.Updated exclusions section.Updated cautions section to include GI perforation.Updated renal and hepatic dose modification info in line with Giraud et al 2023.Updated in line with NCCP standardisation. | |

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i]The rapid infusion is an unlicensed means of administration of bevacizumab for the indications described above, in Ireland. Patients should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" means of administration has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.

[ii] Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects. Risk factors for developing anthracycline-induced cardiotoxicity include:

• high cumulative dose, previous therapy with other anthracyclines or anthracenediones

• prior or concomitant radiotherapy to the mediastinal/pericardial area

• pre-existing heart disease

• concomitant use of other potentially cardiotoxic drugs In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient