EC-Paclitaxel (Breast)
(Epirubicin and Cyclophosphamide and Paclitaxel)

Indication
Adjuvant or neo-adjuvant treatment for high risk early stage and locally advanced breast cancer.

(NICE NG101)

ICD-10 codes
Codes with a prefix C50

Regimen details

Cycles 1-3 (EC)

Day	Drug	Dose	Route
1	Epirubicin	100mg/m^2	IV bolus
1	Cyclophosphamide	500mg/m^2	IV bolus

Cycles 4-7 (weekly paclitaxel)

Day	Drug	Dose	Route
1, 8, 15	Paclitaxel	80mg/m^2	IV infusion

Cycle frequency
21 days

Number of cycles
3 x cycles of EC followed by 4 x cycles of weekly paclitaxel

Administration
Epirubicin and cyclophosphamide are administered by slow IV bolus into the arm of a fast running drip of sodium chloride 0.9%. Cyclophosphamide may also be given as an IV infusion in 250-500mL sodium chloride 0.9% over 30 minutes.

Paclitaxel should be administered first.

Paclitaxel is administered in a 250-500mL sodium chloride 0.9% non-PVC infusion bag with a 0.22 micron in-line filter over 1 hour.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of paclitaxel. Facilities for the treatment of hypotension and bronchospasm **must** be available.

If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve restarted at a slower infusion rate. Chlorphenamine 10mg IV may be administered. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of paclitaxel or carboplatin and appropriate therapy should be initiated

Pre-medication

30 minutes prior to each paclitaxel infusion:
Chlorphenamine 10mg IV slow bolus
Dexamethasone 8mg IV slow bolus

Emetogenicity

EC cycles: moderate - high emetic potential
Paclitaxel cycles: low-moderate emetic potential

Additional supportive medication

Mouthwashes as per local policy
Proton-pump inhibitor if required
Loperamide if required.
Scalp cooling may be offered.
Primary GCSF prophylaxis required for EC cycles on days 2-8

Extravasation

Epirubicin is a vesicant (Group 5)
Cyclophosphamide is neutral (Group 1)
Paclitaxel is a vesicant (Group 5)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days

ECHO or MUGA if significant cardiac history or previous anthracycline treatment.

Investigations – pre subsequent EC cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days

Investigations – pre subsequent weekly paclitaxel cycles

Investigation	**Validity period** (or as per local policy)
FBC	24 hours*
U+E (including creatinine)	96 hours
LFTs	96 hours

*Additional FBC within 24 hours of day 8 and 15 doses.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine Clearance (CrCl)	> 20 mL/min
Bilirubin	≤ 1.0 ULN
AST/ALT	≤ 2.0 x ULN (see below for further information)
Alkaline Phosphatase	≤ 2.5 x ULN

Dose modifications

- **Haematological toxicity**

EC cycles:

If neutrophils <1.0 x 10^9/L and/or platelets <100 x 10^9/L delay 1 week or until recovery. If febrile neutropenia despite GCSF or neutrophils < 0.5 x 10_9/L for more than 1 week consider reducing doses to 80% for future cycles.

Weekly paclitaxel cycles:

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Paclitaxel dose**
≥ 1.0	and	≥ 100	100%
< 1.0	or	< 100	Delay 1 week (or until recovery)*
< 1.0	and	< 100	Delay 1 week (or until recovery) then reduce dose to 70mg/m2*

*Omit paclitaxel if occurring on **day 8 or 15**

In the case of febrile neutropenia (neutrophils < 0.5 × 109/L and fever > 38.5°C requiring IV antibiotics) reduce paclitaxel to 60mg/m^2 and carboplatin by 1 x AUC for all subsequent doses.

- **Renal impairment**

CrCl (mL/min)	**Cyclophosphamide dose**
> 20	100%
10-20	75%
<10	50%

There is no data available on the use of epirubicin in severe renal impairment. Consider dose reduction if CrCl <10mL/min (consultant decision).

No dose modification required for paclitaxel.

- **Hepatic impairment**

EC cycles:

Bilirubin (x ULN)		**AST/ALT** (x ULN)		**Alkaline phosphatase** (xULN)	**Epirubicin dose**
< 1.5	and	≤ 2.0	and	≤ 2.5	100%
1.5 - < 3	or	> 2.0 -3.5	or	> 2.5 - <5	50%
≥3 - 5	or	> 3.5	or	5-10	25%
> 5			or	> 10	Omit

Cyclophosphamide is not recommended if bilirubin > 1.5 x ULN or AST/ALT > 3 x ULN (consultant decision).

Paclitaxel:

Paclitaxel is not recommended in severe hepatic impairment. If bilirubin < 1.5 x ULN and AST/ALT < 5 x ULN proceed with 100% dose. For more severe hepatic impairment, treatment may only proceed on consultant's decision, at a reduced dose with weekly monitoring of LFTs.

- **Other toxicities**

EC:
For grade 3 or 4 mucositis/stomatitis – delay until resolved to ≤ grade 1 and reduce epirubicin to 80% dose.

Carboplatin + weekly paclitaxel:

Toxicity	Definition	Paclitaxel dose
Fatigue	Grade 3	1st occurrence – reduce to 70mg/m2 for all subsequent doses or omit.
Neuropathy	Grade 2	1st occurrence – reduce to 70mg/m2 for all subsequent doses or omit.
	Grade ≥ 3	Discuss with consultant.

Any other grade 3 or 4 toxicity- discuss with consultant.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Secondary malignancy
Myelosuppression
Infusion related reactions
Anaphylaxis
Teratogenicity
Infertility/Early menopause
Cardiotoxicity
Peripheral neuropathy

- **Frequently occurring side effects**

Diarrhoea
Constipation
Fatigue
Nausea and vomiting
Myelosuppression
Stomatitis and mucositis
Arthralgia and myalgia
Alopecia

- **Other side effects**

Fluid retention
Red urine (for 24 hours post epirubicin)
Deranged liver function
Phlebitis
Skin toxicity
Nail changes
Taste disturbances
Bladder irritation

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Phenytoin: requires close monitoring if using concurrently.

Cyclophosphamide:
Amiodarone: increased risk of pulmonary fibrosis – avoid if possible
Azathioprine: increased risk of hepatotoxicity
Clozapine: increased risk of agranulocytosis – avoid concomitant use
CYP2B6 and CYP3A4 inhibitors (Nevirapin, Ritonavir): co-administration may reduce the efficacy of cyclophosphamide
Digoxin tablets: reduced absorption – give as liquid form
Indapamide: prolonged leucopenia is possible - avoid
Itraconazole: may increase adverse effects of cyclophosphamide
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Paclitaxel:
Clozapine: increased risk of agranulocytosis
Paclitaxel is a CYP 2C8/9 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

Additional comments

Epirubicin has a life time maximum cumulative dose of 900mg/m^2

References

- Summary of Product Characteristics Epirubicin (Medac) accessed 23 November 2023 via www.medicines.org.uk
- Summary of Product Characteristics Cyclophosphamide (Sandoz) accessed 23 November 2023 via www.medicines.org.uk
- Summary of Product Characteristics Paclitaxel (Hospira) accessed 23 November 2023 via www.medicines.org.uk
- National Institute of Health and Care Excellence. NG101. Accessed 23 November 2023 via www.nice.org.uk
- Moebus, V. et al. Intense Dose-Dense Sequential Chemotherapy With Epirubicin, Paclitaxel, and Cyclophosphamide Compared With Conventionally Scheduled Chemotherapy in High-Risk Primary Breast Cancer: Mature Results of an AGO Phase III Study. J Clin Onc 2010:28 (17):2874-2880.

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