Indication	Neo-adjuvant or adjuvant treatment of triple negative and/or BRCA +ve breast cancer
Treatment Intent	Adjuvant Neo-adjuvant
Frequency and number of cycles	EC (epirubicin and cyclophosphamide) every 14 days for 4 cycles followed by weekly carboplatin and weekly paclitaxel repeated on a 21-day cycle for 4 cycles.
Monitoring Parameters pre-treatment	• Consider using actual BSA • **EC** • ECG should be checked prior to cycle 1 and undertake ECHO/MUGA at baseline if clinically indicated. • Maximum cumulative dose of epirubicin = 950mg/m^2. • Monitor FBC, LFT and U&E at each cycle. • If neuts >/= 1 and PLT>/=100 continue with treatment. If neuts <1 or PLT <100 delay by 1 week. • **Hepatic and renal impairment:** d/w consultant or registrar if bilirubin elevated. Epirubicin: if bilirubin is 24-51 µmol /L give 50%, if bilirubin is 52-85µmol/L give 25%, if bilirubin is >85µmol/L omit. • Dose reduction should be considered if grade 3 or 4 non-haematological toxicity or repeat appearance of grade 2 (except N&V and alopecia). Delay until resolution of toxicity to </= grade 1 • **Paclitaxel/Carboplatin** • EDTA/DTPA should be used to measure GFR prior to cycle 5. C+G may be used to estimate CrCl if there is a delay in obtaining EDTA result, CrCl must be >/=30ml/min. Repeat EDTA if Creatinine clearance drops by 25%. • Monitor U+Es, FBC and LFTs prior to each cycle and on day 8 and 15. • If neuts <1 or PLT <100, consider delaying D1 by 1 week or omitting day 8/15. If neuts >/= 1 and PLT>/= 100 continue with treatment. • GCSF should be considered if more than one delay and/or before dose reduction, or if during preceding cycle, the patient has experienced neuts <0.5 or has had febrile neutropenia. • **Hepatic impairment:** ○ Carboplatin: No dose adjustment required. ○ Paclitaxel: If bilirubin < 1.25 x ULN and transaminase < 10 x ULN, dose at full dose. Otherwise consider dose reduction. Not recommended in severe hepatic impairment. • **Renal impairment:** ○ Carboplatin: stop if CrCl<30ml/min. ○ Paclitaxel: no dose reduction necessary. • **Management of adverse reactions and dose adjustments:** • Patients developing hypersensitivity reactions to Paclitaxel may be re-challenged with full dose Paclitaxel following prophylactic medication (e.g. famotidine 40mg po given 4 hours prior to treatment plus Hydrocortisone 100mg iv and chlorphenamine 10mg iv 30 minutes prior to treatment), then give paclitaxel over 3-6 hours (i.e. starting at over 6 hours and gradually increase rate if possible). If patients experience no hypersensitivity reactions after the first two doses of paclitaxel, remove pre-medication with dexamethasone (unless needed as anti-emetic) and chlorphenamine from dose 3 onwards. • Patients developing hypersensitivity reactions to carboplatin: Mild/moderate reactions (grade 1-2) - If symptoms resolve after treatment with hydrocortisone

	and chlorphenamine, the infusion may be restarted at 50% rate for 30 mins, then, if no further reaction, increase to 100% rate. If symptoms do not resolve after treatment with hydrocortisone and chlorphenamine, do not restart the infusion. At consultant's discretion, patients may be rechallenged at a later date with additional prophylaxis. In the event of further reaction (grade 1-3), stop infusion and consider alternative treatment. Anaphylaxis (grade 4): Follow anaphylaxis protocol. Discontinue permanently and consider alternative treatment. • Dose reduce Paclitaxel by 20% in the event of >/= grade 2 neuropathy and consider a delay until recovery to </= grade 1. • Consider omitting paclitaxel in event of recurrent >/= grade 3 neuropathy or recurrent OR persistent >/=grade 2 neuropathy following a dose reduction. • Dose reduction should be considered if grade 3 or 4 non-haematological toxicity or repeat appearance of grade 2 (except N&V and alopecia). Delay until resolution of toxicity to </= grade 1. **Common drug interactions (for comprehensive list refer to BNF/SPC):** o Avoid concomitant use of paclitaxel with CYP2C8 or CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin) and inhibitors (e.g. ketoconazole erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, nelfinavir). o Carboplatin: Caution with other nephrotoxic drugs. o Caution, ciclosporin increases concentration of epirubicin.
References	KMCC protocol BRE-059 EC followed by Carboplatin & Paclitaxel for Breast Cancer SPC accessed online 23.02.21 https://www.bopa.org.uk/bopa-guidance-on-use-of-h2-antagonists-for-hypersensitivity/ von Minckwitz, G et al; Lancet 2014; 15 (7): 746 – 756 **Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial** Sikov, W et al; JCO 2015; 33 (1): 13 – 21 **Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance)**

NB For funding information, refer to CDF and NICE Drugs Funding List

Cycle 1-4 Repeat every 14 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Dexamethasone	8mg	PO		
	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 min	In 50ml Sodium chloride 0.9%
	EPIRUBICIN	**90mg/m²**	IV	Slow bolus	Through the side of a fast running Sodium Chloride 0.9% intravenous infusion
	CYCLOPHOSPHAMIDE	**600mg/m²**	IV	Slow bolus	Through the side of a fast running Sodium Chloride 0.9% intravenous infusion
TTO	Drug	Dose		Directions	
	Dexamethasone	6mg	PO	OM for 3 days. Take with or just after food, or a meal.	
	Metoclopramide	10mg	PO	10mg TDS for 3 days and then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.	
	Ondansetron	8mg	PO	BD for 3 days	
	Filgrastim	300 mcg or consider dose of 480 mcg if patient > 80kg	SC	OD starting on day 3 for 5 days	

Cycle 5-8 Repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
Day 1,8 & 15	**Give pre-meds 30 minutes prior to paclitaxel**				
	Dexamethasone	8mg (may be reduced to 4mg on subsequent ~~cycles~~ doses)	IV	Bolus	
	Chlorphenamine	10mg	IV	Slow bolus	Through the side of a fast running Sodium Chloride 0.9% intravenous infusion.
	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 min	Sodium chloride 0.9% 50ml
	PACLITAXEL	**80mg/m²**	IV	1 hr	In 250ml Sodium Chloride 0.9% (non-PVC bag and non-PVC administration set) via in-line 0.22 microns filter. Flush with sodium chloride 0.9%
	CARBOPLATIN **Dose = (GFR + 25) x AUC**	**AUC 2 (maximum dose 300mg)**	IV	30 mins	In 250ml - 500ml 5% glucose

TTO Cycle 5-8

TTO	Drug	Dose	Route	Directions
Day 1, 8 & 15	Dexamethasone	4mg	PO	OM for 2 days Take with or just after food, or a meal.
	Metoclopramide	10mg	PO	3 times a day for 3 days, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.