DOCEtaxel, CARBOplatin and Trastuzumab (TCH) - 21 days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adjuvant treatment HER2 positive early breast cancer	C50	00258a	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.

Trastuzumab, DOCEtaxel and CARBOplatin are administered once every 21 days for 6 cycles or until disease progression or unacceptable toxicity develops.
Trastuzumab treatment then continues every 21 days for a total of one year from date of first dose (usually 18 doses of trastuzumab in total, including the initial loading dose).

Alternatively trastuzumab may be administered as a 4mg/kg loading dose on Day 1 of cycle 1 followed by trastuzumab 2mg/kg weekly starting on Day 8 until 3 weeks after the last cycle of chemotherapy. Subsequently trastuzumab 6mg/kg is administered once every 21 days for a total of one year from date of first dose. DOCEtaxel and CARBOplatin are administered one day 1 of cycle 1 and repeated once every 21 days for 6 cycles.

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

Cycle 1

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate
1	1	[a, b,c,] Trastuzumab	8mg/kg	IV infusion Observe post infusion	250ml 0.9% sodium chloride over 90min
2	1	[e,f]DOCEtaxel	75mg/m^2	IV infusion	250ml 0.9% sodium chloride over 60min
3	1	CARBOplatin	AUC 6	IV infusion	500ml glucose 5% over 60 min

Cycles 2 -6

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate
1	1	[a,b,c,] Trastuzumab	6mg/kg	IV infusion Observe post infusion[a]	250ml 0.9% sodium chloride over 30min
2	1	[d,e]DOCEtaxel	75mg/m^2	IV infusion	250ml 0.9% sodium chloride over 60min
3	1	CARBOplatin	AUC 6	IV infusion	500ml glucose 5% over 60 min

[a]Recommended Observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies.

[b]If no adverse reactions use 250ml 0.9% sodium chloride over 30min from cycle 2 onwards

[b]Trastuzumab is incompatible with glucose solution

[d]Primary prophylaxis with G-CSF should be considered to reduce the risk of neutropenic complications with DOCEtaxel (See Adverse Effects/Regimen Specific Complications)

[e] Concentration of final volume should be <0.74mg/ml
Use non-PVC equipment

Cycles 7-18

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate
1	[a,b,c,d]Trastuzumab	6mg/kg	IV infusion Observe post infusion	250ml 0.9% sodium chloride over 30min

OR

Cycle 1

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate
1	1	[a,b,c]Trastuzumab	4mg/kg	IV infusion Observe post infusion	250ml 0.9% sodium chloride over 90min
	8, 15	[a,b,c]Trastuzumab	2mg/kg	IV infusion Observe post infusion	250ml 0.9% sodium chloride over 30min
2	1	[d,e]DOCEtaxel	75mg/m^2	IV infusion	250ml 0.9% sodium chloride over 60min
3	1	CARBOplatin	AUC 6	IV infusion	500ml glucose 5% over 60 min

Cycles 2 -6

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate
1	1, 8, 15	[a,b,c]Trastuzumab	2mg/kg	IV infusion Observe post infusion	250ml 0.9% sodium chloride over 30min
2	1	[d,e]DOCEtaxel	75mg/m^2	IV infusion	250ml 0.9% sodium chloride over 60min
3	1	CARBOplatin	AUC 6	IV infusion	500ml glucose 5% over 60 min

[a]Recommended Observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies.

[b]If no adverse reactions use 250ml 0.9% sodium chloride over 30min from cycle 2 onwards

[c]Trastuzumab is incompatible with glucose solution

[d]Primary prophylaxis with G-CSF should be considered to reduce the risk of neutropenic complications with DOCEtaxel (See Adverse Effects/Regimen Specific Complications)

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Use non-PVC equipment

Cycles 7-18

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate
1	[a,b,c,]Trastuzumab	6mg/kg	IV infusion Observe post infusion	250ml 0.9% sodium chloride over 30min

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)

Reference NCCP regimen 00261 CARBOplatin Monotherapy for information on calculation of CARBOplatin dose.

ELIGIBILITY:

- Indications as above
- HER2 positive as demonstrated by a validated test method
- Node positive or high risk node negative
- Life expectancy > 3months
- ECOG status 0-1
- In EBC, LVEF > 55%* for trastuzumab therapy
  *Many clinical trials have been conducted with LVEF ≥ 50% (1). Clinical judgment should be exercised where patients fall between these two ranges.

EXCLUSIONS:

- Hypersensitivity to DOCEtaxel, CARBOplatin, trastuzumab or any of the excipients.
- Clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months).
- Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction with trastuzumab.
- Significant hepatic dysfunction, contraindicating DOCEtaxel
- Baseline neutrophil count < 1.5 x 10^9/L
- ≥ Grade 2 sensory or motor neuropathy
- Pregnancy
- Breast feeding

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, liver and renal profile. (Ref NCCP regimen 00203 DOCEtaxel Monotherapy 75mg/m^2 for precautions regarding hepatic dysfunction and DOCEtaxel).
- Cardiac function (LVEF using ECHO or MUGA scan)

Regular tests:

- FBC, liver and renal profile
- MUGA scan or echocardiogram every 12 weeks during treatment with trastuzumab and at completion of therapy. Where there are signs of cardiac impairment four to eight weekly checks may be more appropriate.

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:

- Doses are adjusted based on Day 1 counts and previous cycle febrile neutropenia.
- No dose reduction for nadir counts.
- **No reduction of trastuzumab dose for haematologic toxicity.**

Table 1: Dose modification for haematological toxicity

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose DOCEtaxel and CARBOplatin	G-CSF option
$\geq$ 1.5	**and**	$\geq$ 100	100%	
1 -1.49	**and**	$\geq$ 100	75%	100% regimen
< 1.0	**or**	< 100	Delay until ANC $\geq$ 1.5 and platelets $\geq$ 100 then give 75%	Delay until ANC $\geq$ 1.5 and platelets $\geq$ 100 then give 100%

Febrile Neutropenia:

Table 2: Dose modification for febrile neutropenia

Event	Dose reduction option	G-CSF option
1st event	75% of previous cycles dose if Day 1 $\geq$ 1.5 and platelets $\geq$ 100	100% regimen
2nd event	50% of original cycle dose if Day 1 $\geq$ 1.5 and platelets $\geq$ 100	75% regimen
3rd event	Discontinue regimen or switch to G-CSF option	50% regimen

Renal and Hepatic Impairment:

Table 3: Dose modification of DOCEtaxel, trastuzumab and CARBOplatin in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment
DOCEtaxel	No dose reduction necessary	**See note below and Table 4**

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 re-measuring the GFR or to recalculating using Cockcroft & Gault or Wright formulae taking care this does result in a dose reduction	No dose modification required
Trastuzumab	No dedicated studies of trastazumab in patients with renal impairment have been conducted. Based on a population pharmacokinetic (PK) analysis renal impairment was not shown to affect trastuzumab disposition	No dedicated studies of trastazumab in patients with hepatic impairment have been conducted. Probably no dose reduction necessary

DOCEtaxel and hepatic dysfunction:

- DOCEtaxel doses shall be modified for hepatic toxicity. If DOCEtaxel is delayed due to hepatic toxicity, other drugs being used in combination at that time shall also be delayed and administered when DOCEtaxel is resumed.
- Since no data in patients with abnormal bilirubin level treated with lower dose of DOCEtaxel are available, in the event that bilirubin levels are abnormal during the study, the next cycle will be delayed by a maximum of two weeks. If no recovery, the patient should be taken off chemotherapy. Treatment with trastuzumab may continue.
- In the event that AST and/or ALT and/or alkaline phosphatase levels are abnormal in the absence of relapse, the following dose modifications should apply (Table 4).
- Once the dose is reduced due to impaired liver function, no further dose reduction is recommended if no worsening of the parameters is observed.
- In case of recovery of liver function tests on the following cycle, the dose should be re-escalated to the previous dose level.

Table 4: Dose Modification of DOCEtaxel based on hepatic dysfunction

AST / ALT Values	Alkaline Phosphatase Values	Dose Modification
≤ 1.5 x ULN	≤ 5 x ULN	no dose modification
> 1.5 x ULN to ≤2.5 x ULN	≤ 2.5 x ULN	no dose modification

> 2.5 x ULN to ≤5 x ULN	≤ 2.5 x ULN	Reduce dose of DOCEtaxel from 75 to 60mg/m^2
> 1.5 x ULN to ≤ 5 x ULN	> 2.5 x ULN to ≤ 5 x ULN	Reduce dose of DOCEtaxel from 75 to 60 mg/m^2
> 5 x ULN	> 5 x ULN	Dose delay by a maximum of 2weeks. If no recovery to the above figures, patient should go off chemotherapy.

Missed doses of trastuzumab:

- If the patient misses a dose of trastuzumab by one week or less, then the usual maintenance dose of
  6mg/kg should be given as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should then be given according to the previous schedule.

- If the patient misses a dose of trastuzumab by more than one week, a re-loading dose of trastuzumab (8mg/kg) should be given over approximately 90 minutes, at the discretion of the clinician. Subsequent trastuzumab maintenance doses (6mg/kg) should then be given every 3 weeks from that point.

Non-Haematological Toxicity:

Table 5: Dose modification schedule based on adverse events

Adverse reactions	Discontinue	Recommended dose modification
Grade >2 peripheral neuropathy		Decrease dose of **DOCEtaxel** to 60mg/m^2 If the patient continues to experience these reactions at 60mg/m^2, treatment with DOCEtaxel should be discontinued
LVEF drops 10 ejection fraction points from baseline and to below 50%		Withhold treatment with **trastuzumab.** Repeat LVEF after 3 weeks. No improvement or further decline consider discontinuation. Discuss with consultant and refer to cardiologist.
Symptomatic heart failure		Consider discontinuation – refer to cardiology for review. Clinical decision
NCI-CTCAE Grade 4 hypersensitivity reactions	Discontinue	
Grade ≥3 Stomatitis		DOCEtaxel will be reduced from 75 to 60 mg/m^2. If despite dose reduction, stomatitis still occurs at grade ≥ 3, DOCEtaxel will be further reduced from 60 to 50 mg/m^2. No further dose reduction is planned. Trastuzumab may continue without dose reduction.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

DOCEtaxel: Low **(refer to local policy)**
CARBOplatin: High **(refer to local policy)**
Trastuzumab: Minimal **(Refer to local policy)**

PREMEDICATIONS:

DOCEtaxel: Dexamethasone 8 mg PO twice daily for 3 days, starting one day prior to each DOCEtaxel administration unless contraindicated. Patient must receive minimum of 3 doses pre-treatment
Consideration may be given, at the discretion of the prescribing consultant, to the use of a single dose of dexamethasone 20mg IV immediately before chemotherapy where patients have missed taking the oral premedication dexamethasone as recommended by the manufacturer (2,3).

Trastuzumab: Not usually required unless the patient has had a previous hypersensitivity. Paracetamol and antihistamine cover should be considered.
Patient should be educated about the possibility of delayed infusion-related symptoms.

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

Reference
NCCP regimen 00203 DOCEtaxel Monotherapy 75mg/m^2-21 day cycle,
NCCP regimen 00200 Trastuzumab Monotherapy -21 day cycle and
NCCP regimen 00261CARBOplatin Monotherapy
for detailed information on adverse effects/regimen specific complications.

DRUG INTERACTIONS:

- Risk of drug interactions causing increased concentrations of DOCEtaxel with CYP3A inhibitors. Patients should also be counselled with regard to consumption of grapefruit juice.
- Risk of drug interactions causing decreased concentrations of DOCEtaxel with CYP3A inducers.
- A possible interaction with warfarin has been reported. An increased INR and bleeding may occur in patients previously stabilized on warfarin. The interaction was noted in two patients after 8-10 doses of trastuzumab. Increased monitoring of INR is advised while receiving trastuzumab. Inform patient to watch for any bleeding. Modification of the warfarin dose may be needed.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

DOCEtaxel	L01CD02
CARBOplatin	L01XA02
Trastuzumab	L01XC03

REFERENCES:

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Version	Date	Amendment	Approved By
1	10/09/2015		Dr Maccon Keane
2	20/9/2017	Applied new NCCP regimen template, clarified use of G-CSF, administration order and dosing in renal and hepatic impairment	Prof Maccon Keane
3	16/03/2018	Treatment table updated for standardisation and inclusion of other treatment options.	Prof Maccon Keane
4	26/02/2020	Updated DOCEtaxel final volume concentration, standardised CARBOplatin renal impairment guidance, heart failure guidance updated, updated INR monitoring.	Prof Maccon Keane
5	15/07/2020	Amended Trastuzumab administration details in the Treatment table	Prof Maccon Keane
6	9/9/2020	Updated emetogenic potential of Trastuzumab	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.