DOCEtaxel, CARBOplatin and Trastuzumab (TCH) - 21 days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Adjuvant treatment HER2 positive early breast cancer	C50	00258a	N/A

*This applies to post 2012 indications

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 patient's 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). **Refer to NCCP Regimens 00200 Trastuzumab IV Monotherapy - 21 days or 00285 Trastuzumab SC - 21 days.**

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 on day 1 of cycle 1 and repeated once every 21 days for 6 cycles.

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

Table 1: Cycle 1 TCH (three-weekly trastuzumab-IV)

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

Table 2: Cycle 2-6 TCH (three-weekly trastuzumab-IV)

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

[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 NaCl 0.9% over 30 minutes from cycle 2 onwards

[c]Trastuzumab is incompatible with Glucose 5%

[d]Primary prophylaxis with G-CSF should be considered to reduce the risk of neutropenic complications with DOCEtaxel

[e] Concentration of final volume should be <0.74mg/mL Use non-PVC infusion bag

Table 3: Cycle 7-18 TCH (maintenance trastuzumab-IV)

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

ALTERNATIVE TREATMENT SCHEDULES
DOCEtaxel, CARBOplatin and Trastuzumab (weekly-IV) (TCH) - 21 days

Table 4: Cycle 1 TCH (weekly trastuzumab-IV)

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

Table 5: Cycle 2-6 TCH (weekly trastuzumab-IV)

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

[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 NaCl 0.9% over 30 minutes from cycle 2 onwards
[c]Trastuzumab is incompatible with Glucose 5%
[d]Primary prophylaxis with G-CSF should be considered to reduce the risk of neutropenic complications with DOCEtaxel
[e] Concentration of final volume should be <0.74mg/mL Use non-PVC infusion bag.

Cycle 7-18 TCH (maintenance trastuzumab-IV) refer to table 3 above.

OR

DOCEtaxel, CARBOplatin and Trastuzumab (subcutaneous) (TCH) - 21 days

Table 6: Cycles 1-6 TCH (subcutaneous trastuzumab)

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate
1	1	[a,b]Trastuzumab	600mg	SC	Over 2-5 minutes
2	1	[c,d]DOCEtaxel	75mg/m^2	IV infusion	250mL NaCl 0.9% over 60 minutes
3	1	CARBOplatin	AUC 6	IV infusion	500mL Glucose 5% over 30 minutes
[a]The injection site should be alternated between the left and right thigh. New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard. During the treatment course with trastuzumab subcutaneous formulation other medicinal products for subcutaneous administration should preferably be injected at different sites.					
[b]Patients should be observed for 30 minutes after the first injection and for 15 minutes after subsequent injections for signs or symptoms of administration related reactions. Any deviation should be noted in local policies.					
[c]Primary prophylaxis with G-CSF should be considered to reduce the risk of neutropenic complications with DOCEtaxel					
[d]Concentration of final volume should be <0.74mg/mL Use non-PVC infusion bag					

Table 7: Cycle 7-18 TCH (subcutaneous trastuzumab)

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate
1	1	[a,b] Trastuzumab	600mg	SC	Over 2-5 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)

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

ELIGIBILITY:

- Indications as above
- HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay. Please see *Recommendations on Reporting on HER2 Status in Breast Cancer Patients* Available on the NCCP website
- Node positive or high-risk node negative
- ECOG status 0-2

- 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)
- Significant hepatic dysfunction, contraindicating DOCEtaxel
- Baseline neutrophil count < 1.5 x 10^9/L
- Pregnancy
- Breastfeeding
  *If it is felt that the patient may have a major clinical benefit from CARBOplatin, it may in exceptional circumstances be feasible to rechallenge a patient with a prior mild hypersensitivity reaction e.g. using a desensitisation protocol, but only with immunology advice, premedication as advised, and a desensitisation protocol under carefully controlled conditions with resuscitation facilities available and medical and/or ITU/ HDU supervision

CAUTION:

- ≥ Grade 2 sensory or motor neuropathy

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/m²** for precautions regarding hepatic dysfunction and DOCEtaxel)
- Cardiac function (LVEF using ECHO, MUGA scan) if clinically indicated
- Isotope GFR measurement (preferred) or GFR / CrCl estimation

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 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	If patient receiving G-CSF
≥ 1.5	**and**	≥ 100	100%	
1 -1.49	**and**	≥ 100	75%	100% regimen
< 1.0	**or**	< 100	Delay until ANC ≥ 1.5 and platelets ≥ 100 then give 75%	Delay until ANC ≥ 1.5 and platelets ≥ 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 ≥ 1.5 and platelets ≥ 100	100% regimen
2nd event	50% of original cycle dose if Day 1 ≥ 1.5 and platelets ≥ 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	See note below[a]	No dose modification required
Trastuzumab	No dose reduction necessary	No dedicated studies of trastuzumab in patients with hepatic impairment have been conducted. Probably no dose reduction necessary
DOCEtaxel: Renal and hepatic dose modifications – As previously agreed across NCCP regimens CARBOplatin: Renal and hepatic dose modifications – As previously agreed across NCCP regimens Trastuzumab: Renal and hepatic dose modifications from Giraud et al 2023		

[a]Renal dysfunction and CARBOplatin:

- Patients with creatinine clearance values of <60mL/min are at greater risk of developing myelosuppression.
- If GFR between 20 to ≤ 30mL/min, CARBOplatin should be administered with extreme caution
- If GFR ≤ 20mL/min, CARBOplatin should not be administered at all
- If Cockcroft & Gault or Wright formula are used, the dose should be calculated as required per cycle based on a serum creatinine obtained within 48 hrs of drug administration.

If isotope GFR is used, the dose can remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine increases, consideration

should be given to remeasuring the GFR or to estimating it using Cockcroft & Gault or Wright formulae.

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 (three-weekly regimen: 6 mg/kg; weekly regimen: 2mg/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 should be given over approximately 90 minutes (three weekly regimen: 8 mg/kg; weekly regimen: 4 mg/kg), at the discretion of the clinician. Subsequent trastuzumab maintenance doses (three-weekly regimen: 6mg/kg; weekly regimen 2 mg/kg) should then be given according to the three-weekly or weekly schedules respectively.

- If the patient misses a dose of subcutaneous trastuzumab, it is recommended to administer the next 600mg dose (i.e. the missed dose) as soon as possible. The interval between consecutive trastuzumab subcutaneous formulation administrations should not be less than three weeks.

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, discuss with consultant and consider referral to cardiology.
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:

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

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

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

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

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:

- G-CSF support may be required **(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.

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Version	Date	Amendment	Approved By
1	10/09/2015		Dr Maccon Keane
2	20/09/2017	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	09/09/2020	Updated emetogenic potential of Trastuzumab	Prof Maccon Keane
7	09/09/2021	Clarification of requirement for non-PVC infusion bag only.	Prof Maccon Keane
8	04/09/2023	Updated CARBOplatin infusion time. Updated standard wording for CARBOplatin dosing, renal impairment and creatinine value. Updated baseline tests.	Prof Maccon Keane
9	16/04/2025	Regimen reviewed. Updated eligibility section. Addition of cautions section. Subcutaneous administration table added. Amended table 2 in line with Giraud et al (2023) Updated regimen in line with NCCP standardisation.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.