Chemotherapy Protocol

BREAST CANCER

CYCLOPHOSPHAMIDE-EPIRUBICIN-DOCETAXEL-PERTUZUMAB - TRASTUZUMAB IV (EC-DPH IV)

Regimen

- Breast Cancer – Cyclophosphamide-Epirubicin-Docetaxel-Pertuzumab IV-Trastuzumab IV (EC-DPH)

Indication

- Neo-adjuvant / adjuvant therapy of breast cancer
- Please refer to the most up to date Bluteq eligibility criteria for pertuzumab and trastuzumab before prescribing
- WHO Performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Cyclophosphamide	Dysuria, haemorrhagic cystitis, taste disturbances
Epirubicin	Cardio-toxicity, urinary discolouration (red)
Docetaxel	Hypersensitivity, fluid retention, neuropathy, joint pains, nail changes, fatigue
Pertuzumab	Diarrhoea, hypersensitivity reactions, headache, reduced appetite, dyspnoea, cough, vomiting, nausea, constipation, rash, pain, oedema, fatigue, asthenia, cardiotoxicity
Trastuzumab	Cardio toxicity, acute respiratory distress syndrome, infusion related effects

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

Monitoring

Regimen

- FBC, U&E's and LFT's prior to day 1 for cycles containing cyclophosphamide, epirubicin and docetaxel. During the administration of trastuzumab with pertuzumab alone this may be reduced to once every three months.
- Ensure adequate cardiac function before and at regular intervals during treatment. Baseline LVEF should be measured, particularly in patients with a history of cardiac problems or in the elderly. An echocardiogram should be conducted before cycle four and then three monthly thereafter.

- HER2 status before initiating therapy

Dose Modifications

The dose modifications listed are for haematological, liver and renal function only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped. The following guidelines apply to chemotherapy only**.**

Please discuss all dose reductions / delays with the relevant consultant before prescribing if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Haematological

Prior to prescribing the following treatment criteria must be met on day 1 of treatment.

Criteria	Eligible Level
Neutrophils	equal to or more than $1x10^9$/L
Platelets	equal to or more than $100x10^9$/L

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80g/l)

In the adjuvant / neo-adjuvant setting always check with the relevant consultant before delaying or reducing the dose in response to a toxicity.

If counts on day one are below these criteria for neutrophils and platelets then delay treatment for seven days. Treatment should only be re-started when these levels are reached. Treatment may be resumed at the original dose or reduce the dose of cyclophosphamide and epirubicin to 80% of the original dose where a NCI-CTC grade 3 or above haematological event has occurred. Consider stopping the docetaxel. If a second episode of neutropenia and / or thrombocytopenia occurs, despite dose reduction or the time to reach the eligible level is longer than seven days consider changing or stopping therapy.

No dose modifications for haematological toxicity are necessary for pertuzumab or trastuzumab. If treatment is not tolerated it should be stopped.

Kidney Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cyclophosphamide	more than 20	100
	10-20	75
	Less than 10	50
Docetaxel	No dose adjustment necessary	
Epirubicin	Dose reduce in severe impairment only	
Pertuzumab	The safety and efficacy of pertuzumab has not been established in renal impairment	
Trastuzumab	No dose adjustment necessary	

Liver Impairment

Drug	Recommendation	
Cyclophosphamide	Dose reduction may not be necessary	
Epirubicin	**Bilirubin (umol/L)**	**Dose (% of original)**
	24-51	50
	52-85	25
	85 or greater	Contra-indicated
	If AST 2-4 x ULN and bilirubin 21-51µmol/L give 50% dose , if the AST greater than 4 x ULN or bilirubin greater than 51µmol/L then give 25% dose	
Docetaxel	If the AST / ALT is 1.5xULN and the Alk Phos is 2.5xULN or greater give 75% of the dose. If the bilirubin is above the ULN and / or the AST / ALT is 3.5xULN or greater and the Alk Phos is 6xULN or greater docetaxel is not recommended.	
Pertuzumab	The safety and efficacy of pertuzumab has not been established in hepatic impairment	
Trastuzumab	No dose adjustment necessary	

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Epirubicin

Discontinue epirubicin if cardiac failure develops.

Docetaxel

Peripheral neuropathy at NCI-CTC grade 3 should result in a dose reduction from 75mg/m^2 to 60mg/m^2 once the neuropathy has resolved to NCI-CTC grade 2 or below. If the NCI-CTC grade 3 neuropathy occurred at doses lower than 75mg/m^2 or a NCI-CTC grade 4 toxicity develops consider stopping treatment.

Excessive tearing / lacrimation are related to cumulative docetaxel doses and occur after a median of 400mg/m². Symptomatic treatment with hypromellose 0.3% eye drops four times a day may help. However, if the ocular irritation continues reduce the docetaxel dose to 80% of the original dose in the first instance.

Delay the docetaxel where a NCI-CTC grade 3 cutaneous toxicity is present on day one of the cycle until it resolves to NCI-CTC grade 1 or below. The subsequent doses of docetaxel should be reduced from 75mg/m^2 to 60mg/m^2. If it occurs with a dose of 60mg/m^2 or if there is no recovery after two weeks, docetaxel treatment should be stopped. Where a NCI-CTC grade 3 cutaneous toxicity occurs between cycles with recovery by day one then reduce the docetaxel dose as described. Docetaxel should be stopped in response to a NCI-CTC grade 4 cutaneous toxicity.

Pertuzumab

The diarrhoea can be severe in patients treated with pertuzumab. It is important to ensure patients are given appropriate therapy for the treatment of diarrhoea. This is not included in the regimen on Aria and must be added from the support folder.

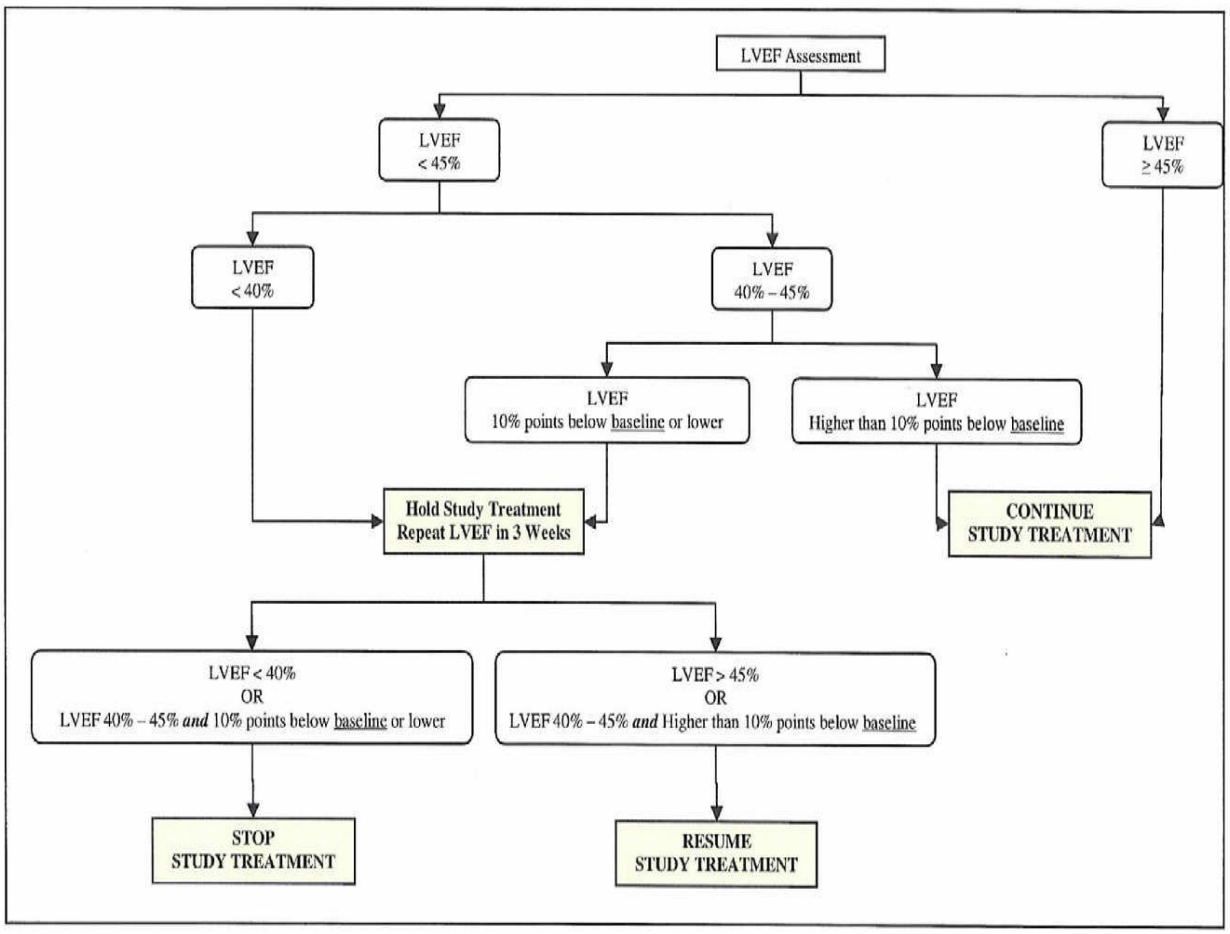
Pertuzumab and Trastuzumab

Cardiac

The LVEF should be fifty or above before starting cycle one of pertuzumab and trastuzumab.

Subsequent Echocardiograms

The flow chart below describes the process to be followed if there is an **asymptomatic** decline in LVEF during pertuzumab and trastuzumab treatment. This is taken from the study protocol as used in the reference section. Study treatment refers to pertuzumab and trastuzumab.



In general patients who develop **symptomatic** cardiac dysfunction should have pertuzumab and trastuzumab discontinued, be commenced on ACE inhibitor therapy and be referred to a cardiologist. Further treatment should be discussed with the relevant oncology consultant.

Regimen

Cyclophosphamide-Epirubicin (EC)

21 day cycle for 3 cycles (cycles 1, 2, 3)

Drug	Dose	Days	Administration
Cyclophosphamide	500mg/m^2	1	Intravenous bolus
Epirubicin	100mg/m^2	1	Intravenous bolus

Followed by;

Docetaxel-Pertuzumab-Trastuzumab

21 day cycle for 4 cycles

Cycle 4

Docetaxel is highly myelosuppressive and in those with poor bone marrow reserves (for example due to extensive prior treatment, bone metastasis or extensive skeletal radiation) consider a starting dose of 55mg/m² with a view to increase to 75mg/m² if well tolerated.

Drug	Dose	Days	Administration
Docetaxel	75mg/m^2	1	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
Pertuzumab	840mg	1	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
Trastuzumab	8mg/kg	1	Intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes

Followed by;

Cycle 5, 6, 7

Drug	Dose	Days	Administration
Docetaxel	75mg/m^2	1	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
Pertuzumab	420mg	1	Intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes
Trastuzumab	6mg/kg	1	Intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

Cycles 8-21 inclusive

Drug	Dose	Days	Administration
Pertuzumab	420mg	1	Intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes
Trastuzumab	6mg/kg	1	Intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

Dose Information

- Cyclophosphamide will be dose banded in accordance with the national dose bands (20PM).
- Epirubicin will be dose banded in accordance with the national dose bands (2PM).
- The maximum lifetime cumulative dose of epirubicin is 900mg/m².
- Docetaxel will be dosed banded in accordance with the national dose bands
- Docetaxel is highly myelosuppressive and in those with poor bone marrow reserves (for example due to extensive prior treatment, bone metastasis or extensive skeletal radiation) consider a starting dose of 55mg/m² with a view to increase to 75mg/m² if well tolerated.
- If the time between two sequential infusions of pertuzumab is less than six weeks, the 420mg dose should be administered as soon as possible without regard to the next planned dose. If the time between two sequential infusions is 6 weeks or more, the initial loading dose of 840mg should be re-administered as a 60 minute intravenous infusion followed every 3 weeks thereafter by a maintenance dose of 420 mg administered over a period of 30 to 60 minutes.
- Trastuzumab will be dose rounded to the nearest 50mg (up if halfway)
- If the patient misses a dose of trastuzumab by seven days 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 be given according to the previous schedule
- If the patient misses a dose of trastuzumab by more than seven days, a re-loading dose of 8mg/kg should be given over 90 minutes. Subsequent maintenance doses should then be given every 21 days from that point

Administration Information

- Hypersensitivity reactions tend to occur with the first or second infusion of docetaxel. Docetaxel infusions should be interrupted for minor symptoms such as flushing or localised rashes. If these resolve promptly (within 5 minutes) the infusion may be restarted at a lower rate with intensive monitoring. Immediately discontinue the infusion for severe reactions which include profound hypotension, bronchospasm and generalised erythema.

- Docetaxel doses of more than 200mg should be diluted in 500ml sodium chloride 0.9% (maximum concentration 0.74mg/ml)

- Pertuzumab has been associated with hypersensitivity and infusion related reactions. Patients should be observed for 60 minutes after the first infusion and for 30 – 60 minutes after subsequent infusions. If patients have tolerated the first two infusions with no infusion related reactions consideration can be given to reducing this observation period.

- Trastuzumab is associated with hypersensitivity reactions. The SPC recommends patients should be observed for six hours following the start of the first infusion of trastuzumab and for two hours following the start of subsequent infusions. In practice these times have been reduced. If the patient has tolerated the first two infusions with no infusion related effects consideration can be given to reducing or stopping this observation period.

Extravasation

- Cyclophosphamide – neutral
- Epirubicin – vesicant
- Docetaxel - exfolliant
- Pertuzumab – neutral
- Trastuzumab - neutral

Additional Therapy

- **EC**

  EC antiemetics day 1

  15-30 minutes prior to chemotherapy;

  - aprepitant 125mg oral
  - dexamethasone 4mg oral or intravenous
  - ondansetron 8mg oral or intravenous

As take home medication

  - aprepitant 80mg once a day for 2 days
  - dexamethasone 2mg twice a day for 3 days oral
  - metoclopramide 10mg three times a day when required oral
  - ondansetron 8mg twice a day for 3 days oral

Growth factor according to local formulary choice. For example;

- filgrastim or bioequivalent 30 million units once a day subcutaneous for five days starting on day five of the cycle
- lenograstim or bioequivalent 33.6 million units once a day subcutaneous for five days starting on day five of the cycle

- pegfilgrastim or bioequivalent 6mg once a day subcutaneous on day two of the cycle

- Docetaxel

  15-30 minutes prior to chemotherapy with **docetaxel**

  - metoclopramide 10mg oral or intravenous

  As take home medication

  - metoclopramide 10mg three times a day when required oral

- To prevent fluid retention and hypersensitivity reactions prescribe dexamethasone 8mg twice a day orally for three days starting 24 hours before the docetaxel administration. On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg, or nearest equivalent dose, once only intravenous bolus.

- For treatment of pertuzumab or trastuzumab infusion reactions 'once only when required' doses of the following should be prescribed;

  - chlorphenamine 10mg intravenous
  - hydrocortisone 100mg intravenous
  - paracetamol 1000mg once oral

- Mouthwashes according to local or national policy on the treatment of mucositis

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

References
1.von Minckwitz G, Proctor M, de Azambuja et al. Adjuvant pertuzumab and trastuzumab in early HER 2 positive breast cancer. N Engl J Med 2017; 377 (2): 122-131.
2. Ramshorst M, van der Voot A, van Werkhoven E et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncology 2018: 19 (12); 1630-1640

REGIMEN SUMMARY

Cyclophosphamide-Epirubicin-Paclitaxel-Pertuzumab IV-Trastuzumab IV (EC-DPH IV)

Cycle 1, 2

1. Aprepitant 125mg oral

2. Dexamethasone 4mg oral or intravenous

3. Ondansetron 8mg oral or intravenous

4. Epirubicin 100mg/m² intravenous bolus over 10 minutes

5. Cyclophosphamide 500mg/m² intravenous bolus over 10 minutes

Take Home Medicines

6. Aprepitant 80mg once a day oral for 2 days starting on day 2 of the cycle
   Administration Instructions
   Take 80mg once a day for 2 days starting on day 2 of the cycle

7. Dexamethasone 2mg twice a day for 3 days oral starting on day two of the cycle
   Administration Instructions
   Take 2mg twice a day (morning and lunch) for 3 days starting on day two of the cycle

8. Metoclopramide 10mg three times a day when required oral
   Administration Instructions
   When required for nausea. Please supply five days or an original pack if appropriate.

9. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of the cycle
   Administration Instructions
   Take 8mg twice a day for three days starting on the evening of day one of the cycle

10. Growth factor according to local formulary choice.
    Administration Instructions
    Dispense according to local formulary choices;
    - filgrastim or bioequivalent 30 million units once a day subcutaneous for 5 days starting on day 5 of the cycle
    - lenograstim or bioequivalent 33.6million units once a day subcutaneous for 5 days starting on day 5 of the cycle
    - pegfilgrastim or bioequivalent 6mg once a day subcutaneous on day 2 of the cycle

Cycle 3

11. Aprepitant 125mg oral

12. Dexamethasone 4mg oral or intravenous

13. Ondansetron 8mg oral or intravenous

14. Epirubicin 100mg/m² intravenous bolus over 10 minutes

15. Cyclophosphamide 500mg/m² intravenous bolus over 10 minutes

Take Home Medicines

16. Aprepitant 80mg once a day oral for 2 days starting on day 2 of the cycle
    Administration Instructions
    Take 80mg once a day for 2 days starting on day 2 of the cycle

17. Dexamethasone 2mg twice a day for 3 days oral starting on day two of the cycle
    Administration Instructions
    Take 2mg twice a day (morning and lunch) for 3 days starting on day two of the cycle

18. Dexamethasone 8mg twice a day oral for 3 days starting the day before the docetaxel infusion

19. Metoclopramide 10mg three times a day when required oral
    Administration Instructions
    When required for nausea. Please supply five days or an original pack if appropriate.

20. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of the cycle
    Administration Instructions
    Take 8mg twice a day for three days starting on the evening of day one of the cycle

21. Growth factor according to local formulary choice.
    Administration Instructions
    Dispense according to local formulary choices;
    - filgrastim or bioequivalent 30 million units once a day subcutaneous for 5 days starting on day 5 of the cycle
    - lenograstim or bioequivalent 33.6million units once a day subcutaneous for 5 days starting on day 5 of the cycle
    - pegfilgrastim or bioequivalent 6mg once a day subcutaneous on day 2 of the cycle

Docetaxel-Pertuzumab-Trastuzumab

Cycle 4

22. Pertuzumab 840mg intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
    Administration Instructions
    The first infusion of pertuzumab should be given over 60 minutes. If this is well tolerated subsequent infusions may be given over 30 minutes

23. Trastuzumab 8mg/kg intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes
    Administration Instructions
    The first infusion of trastuzumab must be administered over 90 minutes. If this is well tolerated administer subsequent infusions over 30 minutes

24. Metoclopramide 10mg oral or intravenous

25. Docetaxel 75mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
    Administration Instructions
    Ensure the patient has taken the dexamethasone pre-medication the day before and the day of docetaxel administration (and the day after). On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg (or equivalent dose) IV stat 15-30 minutes before chemotherapy. If the patient has already taken a dose of dexamethasone do not administer this dose.

26. Chlorphenamine 10mg intravenous when required for infusion related reactions

27. Hydrocortisone 100mg intravenous when required for infusion related reactions

28. Paracetamol 1000mg oral when required for infusion related reactions
    Administration Instructions
    Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses

Take Home Medicines (Day 1 only)

29. Dexamethasone 8mg twice a day oral for 3 days starting the day before the docetaxel infusion

30. Metoclopramide 10mg three times a day when required oral

31. Loperamide 4mg after the first loose stool and 2mg after each subsequent loose stool to a maximum of 16mg in 24 hours
    Administration Instructions
    Take 4mg after the first loose stool and then 2mg after each subsequent loose stool to a maximum of 16mg in 24 hours. Please supply one original pack size

Cycle 5, 6

32. Pertuzumab 420mg intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
    Administration Instructions
    The first infusion of pertuzumab should be given over 60 minutes. If this is well tolerated subsequent infusions may be given over 30 minutes

33. Trastuzumab 6mg/kg intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes
    Administration Instructions
    The first infusion of trastuzumab must be administered over 90 minutes. If this is well tolerated administer subsequent infusions over 30 minutes

34. Metoclopramide 10mg oral or intravenous

35. Docetaxel 75mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
    Administration Instructions
    Ensure the patient has taken the dexamethasone pre-medication the day before and the day of docetaxel administration (and the day after). On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg IV stat, or equivalent dose, 15-30 minutes before chemotherapy

36. Chlorphenamine 10mg intravenous when required for infusion related reactions

37. Hydrocortisone 100mg intravenous when required for infusion related reactions

38. Paracetamol 1000mg oral when required for infusion related reactions
    Administration Instructions
    Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses

Take Home Medicines (Day 1 only)

37. Dexamethasone 8mg twice a day oral for 3 days starting the day before the docetaxel infusion

38. Metoclopramide 10mg three times a day when required oral

Cycle 7

39. Pertuzumab 420mg intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
    Administration Instructions
    The first infusion of pertuzumab should be given over 60 minutes. If this is well tolerated subsequent infusions may be given over 30 minutes

40. Trastuzumab 6mg/kg intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes
    Administration Instructions
    The first infusion of trastuzumab must be administered over 90 minutes. If this is well tolerated administer subsequent infusions over 30 minutes

41. Metoclopramide 10mg oral or intravenous

42. Docetaxel 75mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
    Administration Instructions
    Ensure the patient has taken the dexamethasone pre-medication the day before and the day of docetaxel administration (and the day after). On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg IV stat, or equivalent dose, 15-30 minutes before chemotherapy

43. Chlorphenamine 10mg intravenous when required for infusion related reactions

44. Hydrocortisone 100mg intravenous when required for infusion related reactions

45. Paracetamol 1000mg oral when required for infusion related reactions
    Administration Instructions
    Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses

Take Home Medicines (Day 1 only)

37. Metoclopramide 10mg three times a day when required oral

Cycles 8 – 21

Day 1

39. Pertuzumab 420mg intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
    Administration Instructions
    The first infusion of pertuzumab should be given over 60 minutes. If this is well tolerated subsequent infusions may be given over 30 minutes

40. Trastuzumab 6mg/kg intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes
    Administration Instructions
    The first infusion of trastuzumab must be administered over 90 minutes. If this is well tolerated administer subsequent infusions over 30 minutes

41. Chlorphenamine 10mg intravenous when required for infusion related reactions

42. Hydrocortisone 100mg intravenous when required for infusion related reactions

43. Paracetamol 1000mg oral when required for infusion related reactions

Administration Instructions

Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	March 2022	None	Dr Deborah Wright Pharmacist	Dr J Bradbury Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.