## DRUG ADMINISTRATION SCHEDULE

### Cycle One Loading Doses

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Daily Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Paracetamol</td>
<td>1g</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>Ondansetron</td>
<td>8mg</td>
<td>Oral /Slow bolus/15 min infusion</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>Pertuzumab</td>
<td>840mg</td>
<td>IV Infusion</td>
<td>250ml sodium chloride 0.9% over 60 minutes</td>
</tr>
</tbody>
</table>

Pertuzumab and Herceptin can be given in either order must observe for 30 to 60 minutes between doses.

| Day 1 or 2* | Paracetamol     | 1g         | Oral                                       |                                     |
| Day 1 or 2* | Ondansetron     | 8mg        | Oral /Slow bolus/15 min infusion           |                                     |
| Day 1 or 2* | Herceptin (Trastuzumab) | 8mg/kg     | IV Infusion                                | 250ml sodium chloride 0.9% over 90 minutes |
| Day 1 or 2* | Docetaxel       | 75mg/m²    | IV Infusion                                | 250ml sodium chloride 0.9% over 60 minutes |

*Ondansetron IV must be infused over 15 minutes in patients over 65 years of age.

*Some units may choose to give 1st cycle pertuzumab and herceptin doses on separate days.

### Maintenance Dose Cycle 2 onwards

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Daily Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Paracetamol</td>
<td>1g</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>Pertuzumab</td>
<td>420mg</td>
<td>IV Infusion</td>
<td>250ml sodium chloride 0.9% over 60 minutes</td>
</tr>
</tbody>
</table>

Observe for 30 to 60 minutes between doses.

| Day 1 | Herceptin (Trastuzumab) | 6mg/kg     | IV Infusion                                | 250ml sodium chloride 0.9% over 90 minutes |
| Day 1 | Ondansetron          | 8mg        | Oral /Slow bolus/15 min infusion           |                                     |
| Day 1 | Docetaxel            | 75mg/m²    | IV Infusion                                | 250ml sodium chloride 0.9% over 60 minutes |

*Ondansetron IV must be infused over 15 minutes in patients over 65 years of age.

<table>
<thead>
<tr>
<th>Day -1 to day 2</th>
<th>Drug</th>
<th>Daily Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>8mg BD</td>
<td>Oral</td>
<td>For 3 days prior to next cycle of chemotherapy</td>
<td></td>
</tr>
</tbody>
</table>

*PRECAUTION: In order to reduce the risk of medication errors it is recommended that all trastuzumab products are referred to by brand name, i.e Herceptin IV
CYCLE LENGTH AND NUMBER OF DAYS
Herceptin, Pertuzumab and Docetaxel are given every three weeks.
6 cycles of triple therapy are indicated initially. Docetaxel is stopped after 6 cycles. Trastuzumab and pertuzumab as dual therapy are continued until disease progression.

TREATMENT BREAKS
If a patient misses a dose of Herceptin IV by more than 1 week (i.e. has a 4 week treatment break) then re-loading with Herceptin is necessary.

If a patient misses a dose of Pertuzumab by more than 3 weeks (i.e. has a 6 week treatment break) then re-loading with Pertuzumab is necessary.

No treatment breaks of more than 4 weeks are allowed. Should treatment breaks be required, then an Individual Funding Request must be submitted as per CDF processes

APPROVED INDICATIONS
Patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

This regime is approved by Cancer Drug Fund for the first line treatment of locally advanced or metastatic breast cancer where all the following criteria are met:
1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
2. Locally advanced or metastatic breast cancer
3. HER2 3+ or FISH positive
4. PS 0 or 1
5. Any adjuvant HER2 therapy should have been completed more than 12 months prior to metastatic diagnosis
6. No prior treatment with chemotherapy or HER2 therapy for metastatic disease
7. To be given as first line treatment in combination with docetaxel and trastuzumab

NOTE: not to be used beyond first disease progression outside the CNS. Do not discontinue if disease progression is within the CNS alone

**Prior to prescribing all patients MUST be registered with the Cancer Drug Fund**

EXCLUSION CRITERIA
Herceptin is contraindicated in patients with severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

If LVEF is <40% or 40-45% associated with ≥ 10% points below the pretreatment value, Pertuzumab and Herceptin should be withheld and a repeat LVEF assessment performed within approximately 3 weeks.
PREMEDICATION
Oral Dexamethasone as above

RECOMMENDED TAKE HOME MEDICATION
Oral Ondansetron 8mg Twice Daily for 2 to 3 days. Note this may not be required when docetaxel has stopped
Oral Dexamethasone (premedication as above)
Oral Metoclopramide 10mg Three Times Daily when required

INVESTIGATIONS / MONITORING REQUIRED
Pre-treatment: FBC, U&Es, LFTs, HER2 test, Cardiac assessment including a history and a physical examination (esp. in those with prior AC exposure), ECG, Echocardiogram +/- MUGA to assess LVEF
Prior to each cycle: FBC, U&Es, LFTs
Every 3-4 months Cardiac function (ECHO/MUGA) to assess LVEF
During Infusions Observe for fevers and chills or other infusion-related symptoms for at least 60 minutes after the first Herceptin and pertuzumab infusion, and for 30-60 minutes after subsequent infusions. Note the SPC recommends 6 hours observation after 1st IV Herceptin dose, if patient is released ahead of this times, they must be counselled about the possibility of delayed infusion-related symptoms

ASSESSMENT OF RESPONSE
Metastatic: Tumour size and patient symptomatic response.

REVIEW BY CLINICIAN
To be reviewed by a Nurse, Pharmacist or Clinician before every cycle.

NURSE / PHARMACIST LED REVIEW
On cycles where not seen by clinician.

ADMINISTRATION NOTES
- Make sure the patient has taken their oral dexamethasone premedication as Docetaxel has been known to produce hypersensitivity reactions. Steroid co-medication will also reduce the risk of fluid retention and skin reactions.
- Facilities to treat anaphylaxis MUST be present when the chemotherapy is given.
- Patients should be observed closely for hypersensitivity reactions. Severe hypersensitivity, including anaphylaxis, has been observed in clinical trials.
- Treatment does not need to be stopped for minor hypersensitivity e.g. reactions, flushing, localised rash. Must be stopped for major reactions, e.g. hypotension, dyspnoea, angioedema or generalised urticaria.
- Patients treated with Pertuzumab, Herceptin and Docetaxel are at increased risk of febrile neutropenia, especially during the first 3 cycles of treatment. This may be associated with the higher incidence of mucositis and diarrhoea in these patients. Symptomatic treatment for mucositis and diarrhoea should be considered where necessary.
EXTRAVASATION  See NECN/ Local Policy

TOXICITIES

- Alopecia
- Anaphylaxis and hypersensitivity reactions, e.g. Hypersensitivity, Hypotension and bradycardia, Dizziness
- Cardiotoxicity
- Decreased appetite
- Deranged LFT’s
- Diarrhoea
- Febrile neutropenia
- Fluid retention syndrome
- Insomnia
- Myalgia, Joint pains /Back pain on administration
- Myelosuppression, particularly, thrombocytopenia, anaemia & neutropenia
- Nausea and Vomiting
- Neuropathy
- Pruritus

DOSE MODIFICATION / TREATMENT DELAYS

Please note that dose reductions of pertuzumab and Herceptin are not routinely recommended. Docetaxel should be dose reduced on toxicity.

Haematological Toxicity:

- Delay 1 week if WBC<3.0, ANC <1.0 Platelets <100
- No dose modification for CTC grade I/II ANC
- Grade III/IV ANC → delay chemotherapy until recovered. On recovery give 20% dose reduction

Non-Haematological Toxicity:

If PS deteriorates to Grade 3 or 4 and on assessment patient is more symptomatic withhold treatment and discuss with Oncologist

Liver Function

- Extreme caution in patients with abnormal liver function or patients with evidence of significant replacement of liver parenchyma by tumour. Seek advice if the bilirubin is raised. If bilirubin is >70 μmol/L Docetaxel is contraindicated.
- If the ALT/AST >1.5x upper limit of normal and the alkaline phosphatase >2.5x upper limit of normal, consider dose reduction to 75mg/m².
- If the bilirubin is abnormal, the AST/ALT >3.5x normal and alkaline phosphatase >6x normal take great care when prescribing docetaxel.

Cardiac Toxicity:

The NECN Breast Guidelines give detailed guidance on management and monitoring of cardiac function during trastuzumab therapy. Navigation through the guidelines may be facilitated by the adoption of a traffic light system summarised below.

Available at http://www.necn.nhs.uk/group/breast-nssg/
LVEF Monitoring
At least 4 monthly for adjuvant patients, metastatic patients can be monitored less frequently (see breast guidelines for details)

<table>
<thead>
<tr>
<th>Green</th>
<th>LVEF above the LLN, no signs or symptoms of CHF and any trastuzumab-related LVEF fall being &lt; 0.10 (10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amber</td>
<td>LVEF between the LLN and 0.40 (40%), with no signs or symptoms of CHF, or a trastuzumab-related LVEF reduction of 0.1 (10%) or more.</td>
</tr>
<tr>
<td>Red</td>
<td>LVEF ≤ 0.40 (40%) or symptoms and signs of cardiac failure.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Pre Chemo</th>
<th>Pre Trastuzumab</th>
<th>During Trastuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green</td>
<td>-</td>
<td>Trastuzumab OK</td>
<td>Trastuzumab OK</td>
</tr>
<tr>
<td>Amber</td>
<td>Consider non-anthracycline chemo. Repeat ECHO before trastuzumab</td>
<td>Wait for green</td>
<td>Continue with ACE inhibitor. (Refer to cardiology if already on ACEi)</td>
</tr>
<tr>
<td>Red</td>
<td>Unlikely to be safe to give trastuzumab</td>
<td>Delay trastuzumab, start ACEi and refer to cardiology</td>
<td></td>
</tr>
</tbody>
</table>

TREATMENT LOCATION
Can be given at Cancer Centre or Cancer Unit

REFERENCES: