PACLitaxel 80 (7 day) and Trastuzumab (21 day) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adjuvant treatment of HER2 positive, node-negative breast cancer of tumour size ≤ 3cm	C50	00815a	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.

PACLitaxel is administered weekly on Days 1, 8 and 15 of a 21 day cycle for 4 cycles (Cycles 1 to 4).
Trastuzumab is administered at a dose of 8 mg/kg on Day 1 of the first cycle, followed by 6 mg/kg from Cycle 2 onwards.
Following completion of the first 4 cycles, treatment with trastuzumab monotherapy is continued to complete one year of trastuzumab therapy.

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

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	**1**	Trastuzumab [a, b, c]	8mg/kg	IV infusion Observe post infusion	250ml 0.9% sodium chloride over 90min	Cycle 1
1	**1**	Trastuzumab [a, b, c]	6mg/kg	IV infusion Observe post infusion	If no adverse reactions use 250ml 0.9% sodium chloride over 30min	Every 21 days from Cycle 2 onwards
2	**1, 8, 15**	PACLitaxel [d, e]	80mg/m^2	IV infusion	250ml 0.9% sodium chloride over 1hr	Every 21 days for 4 cycles

[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]Trastuzumab is incompatible with glucose solution.

[c]Trastuzumab can be substituted with the subcutaneous formulation where this has been approved locally.
Trastuzumab is administered subcutaneously at a dose of 600mg over 2-5minutes.
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.

[d]PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22 µm filter with a microporous membrane.

[e]PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.

ELIGIBILITY:

- Indication as above
- HER2 positive as demonstrated by a validated test method
- Tumour size less than or equal to 3 cm
- Patients should have a pre-treatment LVEF of ≥ 55%
- Many clinical trials have been conducted with LVEF ≥ 50%. Clinical judgment should be exercised where patients fall between these two ranges
- ECOG status 0-2
- Adequate organ function

EXCLUSIONS:

- Hypersensitivity to PACLitaxel, trastuzumab or any of the excipients
- Clinically significant cardiac disease
- Baseline neutrophil count < 1.5 x 10^9/L
- Severe hepatic impairment

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Cardiac function (LVEF using ECHO or MUGA scan)

Regular tests:

- FBC, renal and liver profile
- Cardiac function every 12 weeks. 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.

- 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 (8 mg/kg) should be given over approximately 90 minutes, at the discretion of the clinician. Subsequent trastuzumab maintenance doses (6 mg/kg) should then be given weekly from that point.

Haematological:

Table 1: Dose modifications for PACLitaxel in haematological toxicities

ANC (x10^9/L)		Platelets	Dose	Dose after neutropenic sepsis
≥ 1.5	And	> 90	80mg/m^2	65mg/m^2
*1-1.49	Or	70-90	65mg/m^2	50mg/m^2
< 1	Or	< 70	Delay and reduce next dose to 65mg/m^2 or add G-CSF	Delay

* If the ANC is 1 to 1.49 and patient is fit and well can consider full dose of 80 mg/m^2 at discretion of prescribing Consultant

Renal and Hepatic Impairment:

Table 2: Dose modification of PACLitaxel and trastuzumab in renal and hepatic impairment

Drug	Renal impairment	Hepatic impairment			
PACLitaxel	No recommended dose modifications in renal impairment	**ALT**		**Total bilirubin**	**Dose of PACLitaxel**
		< 10 x ULN	and	≤ 1.25 x ULN	80mg/m^2
		< 10 x ULN	and	1.26-2 x ULN	60mg/m^2
		< 10 x ULN	and	2.01-5 x ULN	40mg/m^2
		≥ 10 x ULN	and/or	> 5 x ULN	Not recommended
Trastuzumab	No dedicated studies of trastuzumab 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 trastuzumab in patients with hepatic impairment have been conducted. Probably no dose reduction necessary.			

Management of adverse events:

Table 3: Dose modification schedule for PACLitaxel based on adverse events

Adverse reactions	Discontinue	Recommended dose modification
Grade 2 motor or sensory neuropathy		Decrease dose by 10mg/m^2
All other grade 2 non-haematological toxicity		Hold treatment until toxicity resolves to ≤ grade 1. Decrease subsequent doses by 10mg/m^2.
≥ Grade 3 reaction	Discontinue	

Table 4: Trastuzumab dose modification schedule based on adverse events

Adverse reactions	Discontinue	Recommended dose modification
LVEF drops ≥ 10 ejection fraction points from baseline and to below 50%		Withhold treatment. 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	
Haematological		Treatment may continue during periods of reversible, chemotherapy-induced myelosuppression. Monitor carefully for any complications of neutropenia.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

PACLitaxel: Low **(Refer to local policy)**
Trastuzumab: Minimal **(Refer to local policy)**

PREMEDICATIONS:

- All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to first dose of PACLitaxel treatment.
- The H_2 antagonist, famotidine, can potentially be omitted from the pre-medication requirements for PACLitaxel but the risk of hypersensitivity with this approach is unknown.
    - Caution is advised particularly for patients receiving PACLitaxel every 3 weeks. It is recommended that if famotidine is omitted that patients are monitored closely for any signs of hypersensitivity. Any hypersensitivity should be managed as per local policy.
    - Where a patient experiences hypersensitivity, consider the use of alternative H_2 antagonists **(Refer to local policy).**

Table 5 outlines suggested premedications prior to treatment with PACLitaxel.

Table 5: Suggested pre-medications prior to treatment with PACLitaxel

Day of treatment	Drug	Dose	Administration prior to PACLitaxel
Day 1	Dexamethasone[a]	8mg IV	30 minutes
Day 1	Chlorphenamine	10mg IV	30 minutes
Day 1	Famotidine	20mg IV	30 minutes
Day 8[b] and thereafter	Dexamethasone[a]	None	
Day 8 and thereafter	Chlorphenamine	10mg IV	30 minutes
Day 8 and thereafter	Famotidine[c]	20mg IV	30 minutes
[a]Dose of dexamethasone may be altered, in the event of hypersensitivity reaction, to 20 mg of dexamethasone orally 12 hr and 6 hr prior to re-challenge with PACLitaxel according to consultant guidance.			
[b]Dose of dexamethasone may be added from day 8 if increased risk or previous hypersensitivity reaction according to consultant guidance.			
[c]Dose of famotidine may be omitted in the absence of hypersensitivity reaction according to consultant guidance.			

OTHER SUPPORTIVE CARE:

- Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities.
- Myalgias and arthralgias may occur with PACLitaxel. Analgesic cover should be considered.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

PACLitaxel:

- **Hypersensitivity:** Severe hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred in <1% of patients receiving PACLitaxel after adequate premedication. In the case of severe hypersensitivity reactions, PACLitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be re-challenged with the drug**.**
- **Extravasation:** PACLitaxel causes pain and tissue necrosis if extravasated **(Refer to local policy).**
- **Neutropenia:** This is the dose limiting toxicity. Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Peripheral neuropathy:** Occurs frequently but the development of severe symptoms is rare.
- **Arthralgia/myalgia:** May be severe in some patients; however, there is no consistent correlation between cumulative dose and infusion duration of PACLitaxel and frequency or severity of the arthralgia/myalgia. Symptoms are usually transient, occurring within 2 or 3 days after PACLitaxel administration, and resolving within days.
- **Cardiac conduction abnormalities:** If patients develop significant conduction abnormalities during PACLitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with PACLitaxel. Hypotension, hypertension, and bradycardia have been observed during PACLitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of PACLitaxel infusion, is recommended.
- **Hepatic Dysfunction:** Patients with hepatic impairment may be at increased risk of toxicity, particularly grade 3-4 myelosuppression.

Trastuzumab:

- **Cardiac toxicity**:
  - Trastuzumab has been associated with moderate to severe cardiac failure. Baseline and 3 monthly cardiac function tests are required during treatment especially for those with prior anthracycline exposure.
  - If LVEF drops ≥ 10 ejection fraction (EF) points from baseline AND to below 50%, treatment should be withheld and a repeat LVEF assessment carried out within approximately 3 weeks. If LVEF has not improved, or declined further, discontinuation of trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.
  - Trastuzumab and anthracyclines should not be given concurrently in combination due to cardiotoxicity risk.

- Trastuzumab may persist in the circulation for up to 7 months after stopping trastuzumab treatment. Patients who receive anthracyclines after stopping trastuzumab may possibly be at increased risk of cardiac dysfunction. If possible, avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

- **Trastuzumab infusion-associated symptoms:** Usually chills and fever may occur. Stop infusion and consider antihistamine cover. When symptoms have resolved the infusion may be recommenced. For serious reactions, discontinue the trastuzumab infusion and provide supportive therapy such as oxygen, beta-agonists and corticosteroids.
- **Pulmonary events:** Severe pulmonary adverse reactions can occur in association with the use of trastuzumab and have been associated with a fatal outcome. These events may occur as part of an infusion-related reaction or with a delayed onset. Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

DRUG INTERACTIONS:

- Risk of drug interactions with CYP3A4 and CYP2C8 inhibitors may cause increased concentrations of PACLitaxel. Patients should also be counselled with regard to consumption of grapefruit juice.
- Risk of drug interactions with CYP3A4 and CYP2C8 inducers may cause decreased concentrations of PACLitaxel.
- 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. An INR prior to starting the trastuzumab is recommended, then every 2 weeks for the first 3 months and then monthly if stable. 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.

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Version	Date	Amendment	Approved By
1	11/05/2023		Prof. Maccon Keane

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