PACLitaxel (80) and Trastuzumab Therapy – 7 day (12 weeks)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adjuvant Treatment of HER2 positive, Node-Negative Breast Cancer of tumour size ≤3cm	C50	00512a	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 and trastuzumab are administered once every 7 days for 12 weeks.

Following completion of the initial 12 week treatment period, treatment with trastuzumab should be continued to complete one year of trastuzumab therapy as follows:

- trastuzumab 2mg/kg every 7 days (ref NCCP regimen 00201 Trastuzumab (IV) monotherapy-7days)
  OR
- trastuzumab 6mg/kg (ref NCCP regimen 00200 Trastuzumab monotherapy-21days) every 21 days

Facilities to treat anaphylaxis MUST be present when trastuzumab is administered.

12 Cycles of PACLitaxel/Trastuzumab

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	[a,b] Trastuzumab	4mg/kg	IV infusion Observe post infusion	250ml 0.9% sodium chloride over 90min	Cycle 1
1	[c,d] PACLitaxel	80mg/m^2	IV infusion	250 ml 0.9% sodium chloride over 1hr	Cycle 1
`1	[a,b] Trastuzumab	2mg/kg	IV infusion Observe post infusion	If no adverse reactions use 250ml 0.9% sodium chloride over 30min	Cycle 2 and further cycles
1	[c,d] PACLitaxel	80mg/m^2	IV infusion	250 ml 0.9% sodium chloride over 1hr	Cycle 2 and further 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]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.

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

ELIGIBILITY:

- Indications as above
- HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay
- Tumour size less than or equal to 3 cm
- 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.
- ECOG status 0-2

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, LFTs, creatinine 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 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 (4 mg/kg) should be given over approximately 90 minutes, at the discretion of the clinician. Subsequent trastuzumab maintenance doses (2 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 in hepatic Impairment

ALT		Total bilirubin	Dose of PACLitaxel
< 10xULN	and	≤ 1.25xULN	80mg/m^2
< 10xULN	and	1.26-2xULN	60mg/m^2
< 10xULN	and	2.01-5xULN	40mg/m^2
≥10xULN	and/or	>5xULN	Not recommended

Non-Haematological Toxicity:

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: 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.

Please refer to:

- NCCP regimen 00226 for information on the adverse effects associated with weekly PACLitaxel therapy.
- NCCP regimen 00201 for information on the adverse effects associated with trastuzumab therapy.

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.

REFERENCES:

1. Tolaney SM, Barry WT et al. Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer. N Engl J Med 2015;372:134-41.
2. Perez A, Rodeheffer R. Clinical Cardiac Tolerability of Trastuzumab. J Clin Oncol 2004;22:322-329.
3. Nissenblatt MJ. Karp GI. Bleeding risk with trastuzumab (Herceptin) treatment JAMA 1999;282:2299- 301
4. Quock J et al. Premedication strategy for weekly paclitaxel. Cancer investigation. Volume 20, 2002 issue 5-6
5. Uptodate infusion reactions to systemic chemotherapy available at https://www.uptodate.com/contents/infusion-reactions-to-systemic-chemotherapy#H37
6. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
7. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
8. NCCP Classification Document for Systemic Anti- Cancer Therapy (SACT) Induced Nausea and Vomiting V4 2022. https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp%20antiemetic%20classification%20document%20v1%202018.pdf
9. PACLitaxel. Summary of Product Characteristics. Last updated: Accessed Nov 2022. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-050-001_21092022103217.pdf
10. Trastuzumab (Herceptin®) Summary of Product Characteristics. Accessed Nov 2022. Available at: https://www.ema.europa.eu/en/documents/product-information/herceptin-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	10/10/2018		Prof Maccon Keane
2	23/10/2019	Standardised table for suggested premedications prior to treatment with PACLitaxel	Prof Maccon Keane
3	24/03/2021	Reviewed. Amended dose modifications for trastuzumab based on adverse events, premedications for paclitaxel and drug interactions.	Prof Maccon Keane
4	29/11/2022	Updated suggested premedications for PACLItaxel	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.