Palbociclib (Breast)

Indication

In combination with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. Patients should not have received previous hormone therapy for locally advanced/metastatic breast cancer.
Previous hormone therapy with anastrozole or letrozole as adjuvant therapy or as neoadjuvant treatment is allowed as long as the patient has had a disease-free interval of 12 months or more since completing treatment with anastrozole or letrozole.
(NICE TA495)

In combination with fulvestrant for hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy if exemestane and everolimus is the most appropriate alternative to a CDK4/6 inhibitor
(NICE TA836)

NB. Patients should be post-menopausal. If pre- or peri- menopausal, prior to starting treatment patients should have undergone ovarian suppression with LHRH agonist treatment or had bilateral oophorectomy.

ICD-10 codes

Codes with a pre fix C50.

Regimen details

Day	Drug	Dose	Route
1-21 (followed by a 7 day break)	Palbociclib	125mg OD	PO

Cycle frequency

28 days.

Palbociclib should be taken for 21 days followed by a 7 day break.

Number of cycles

Until disease progression or unacceptable toxicity.

Administration

Palbociclib is available as 125mg, 100mg and 75mg film coated tablets. The capsules should be swallowed whole and not chewed, crushed or opened. The dose may be taken with or without food.

Grapefruit and grapefruit juice should be **avoided** whilst taking palbociclib.

Patients should be advised to take the dose at approximately the same time each day. If a patient vomits or misses a dose an additional dose should not be taken that day but the next prescribed dose should be taken as planned.

Pre-medication

Nil

Emetogenicity

This regimen has mild emetic potential.

Additional supportive medication

Nil

Extravasation

N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+Es (including creatinine)	14 days
LFTs	14 days

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours and on day 15 for the first 2 cycles*
U+Es (including creatinine)	96 hours
LFTs	96 hours

*If neutrophils <1.0 x 10^9/L or platelets < 50 x 10^9/L where possible repeat on day 1 of planned cycle

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L
CrCl	≥ 30mL/min
Bilirubin	< 1.5 x ULN
AST/ALT	< 3 x ULN

Dose modifications

Dose reductions should follow the table below:

Dose level	Dose
Full dose	125mg OD
First reduction	100mg OD
Second reduction	75mg OD

Dose reductions below 75mg OD are not recommended and if required treatment should be discontinued.

- **Haematological toxicity**

On day 1 neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L.
Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop grade 3 or 4 neutropenia.

Haematological toxicity	Dose
Grade 1-2 (neutrophils ≥ 1.0 x 10^9/L)	No dose modification required.
Grade 3 (neutrophils 0.5- 1.0 x 10^9/L)	**Day 1:** Withhold and repeat FBC. When recovered to ≤ grade 2 start next cycle at the same dose. **Day 15:** Continue to complete cycle and repeat FBC on day 22. Consider dose reduction if not recovered within 7 days or recurrent neutropenia.
Grade 3 (neutrophils 0.5- 1.0 x 10^9/L) with fever / infection	**At any time:** Withhold until recovered to ≤ grade 2. Resume with one dose level reduction.

Grade 4 (neutrophils < 0.5 x 10^9/L)	**At any time:** Withhold until recovered to ≤ grade 2. Resume with one dose level reduction.

- **Renal impairment**

No dose adjustment is required in patients with mild, moderate or severe impairment (CrCl ≥ 15ml/min). Palbociclib has not been studied in patients requiring haemodialysis but no need for dose adjustment is expected.

- **Hepatic impairment**

Palbociclib is extensively metabolised in the liver. In sufficient data is available for patients with moderate/severe hepatic impairment but the recommended dose for patients with severe hepatic impairment (Child Pugh C) is 75mg OD. Discuss with consultant if ALT > 3 x ULN and/or bilirubin >1.5 x ULN

- **Other toxicities**

For any other non-haematological toxicity ≥ Grade 3; withhold until ≤ Grade 1 (≤ Grade 2 if not considered safety risk) then resume with one dose level reduction.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Neutropenia, anaemia, leukopenia.
Infections
Venous thromboembolism
Interstitial lung disease, pneumonitis

- **Frequently occurring side effects**

Neutropenia, anaemia, leukopenia.
Thrombocytopenia
Infections
Fatigue
Nausea and vomiting
Stomatitis
Rash, dry skin
Alopecia
Diarrhoea

- **Other side effects**

Reduced appetite
Dysgeusia
Blurred vision
Dry eyes
Increased transaminases

Significant drug interactions – for full details consult product literature/ reference texts

Strong CYP3A4 inhibitors (e.g. clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole, grapefruit): Concomitant use of strong inhibitors should be avoided due to increased risk of toxicity. If co-administrated is deemed essential the dose of palbociclib should be reduced to 75mg daily and patients closely monitored.

Strong CYP3A4 inducers (e.g. carbamazepine, enzalutamide, phenytoin, rifampin, and St. John's Wort)**:** Concomitant use may reduce the exposure of palbociclib and should therefore be avoided.

CYP3A substrates: palbociclib weakly inhibits CYP3A therefore may increase exposure to CYP3A substrates. Doses of sensitive CYP3A substrates with a narrow therapeutic index (e.g. alfentanil, ciclosporin, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus) may need to be reduced when co-administered.

P-gp substrates (e.g. digoxin, dabigatran, colchicine): Palbociclib may increase exposure to P-gp substrates increasing risk of adverse effects

BCRP substrates (e.g. pravastatin, rosuvastatin, sulfasalazine): Palbociclib may increase exposure to BCRP substrates increasing risk of adverse effects
OCT1 substrates (e.g. metformin): Palbociclib may increase exposure to OCT1 substrates increasing risks of adverse effects.

Additional comments

Women of childbearing potential or their male partners must use a highly effective method of contraception.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

References

- National Institute for Clinical Excellence (TA495) accessed 27 July 2023 via www.nice.org.uk
- National Institute for Clinical Excellence (TA836) accessed 27 July 2023 via www.nice.org.uk
- Summary of Product Characteristics Palbociclib (Pfizer) accessed 27 July 2023 via www.medicines.org.uk
- Finn, R et al; The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. The Lancet Oncology. 2015. Volume 16:1 p25-35.
- Finn, R et al; Palbociclib and letrozole in advanced breast cancer. NEJM 2016 ; 375 : 1925 – 1936.
- Cristofanilli, M. et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016;17(4):425-439

Written/reviewed by: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust)

Checked by: Kate Gregory (Lead pharmacist for SACT Protocols, SWAG Cancer Alliance)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust and SWAG Cancer Alliance)

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