Palbociclib Therapy - 28 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor	C50	00414a	CDS 01/06/2018
Treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with fulvestrant in women who have received prior endocrine therapy	C50	00414b	CDS 01/06/2018

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.

Palbociclib is taken once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days until disease progression or unacceptable toxicity develops.

Day	Drug	Dose	Route and Method of administration	Cycle
1-21	*Palbociclib	125mg daily	PO taken with food, preferably a meal to ensure consistent palbociclib exposure	Every 28 days
*Please note palbociclib should be administered in combination with either an aromatase inhibitor or fulvestrant. In pre-or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.				
Palbociclib should not be taken with grapefruit or grapefruit juice. Pablociclib capsules should be swallowed whole (should not be chewed, crushed, or opened prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.				

ELIGIBILTY:

- Indications as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to palbociclib or any of the excipients
- Pregnancy
- Breastfeeding

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile

Regular tests:

- FBC Day 1 and day 15 of first 2 cycles and as clinically indicated
- FBC day 1 from cycle 3 onwards
- For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, complete blood counts for subsequent cycles should be monitored every 3 months, prior to the beginning of a cycle and as clinically indicated
- Renal and liver profile prior to each cycle

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
- Management of some adverse reactions may require temporary dose interruptions/delays, and/or dose reductions, or permanent discontinuation as per dose reduction schedules provided in Tables 1, 2, and 3

Table 1: Recommended dose modifications of palbociclib for adverse reactions

Dose Level	Dose
Recommended dose	125mg/day
First dose reduction (Dose level -1)	100mg/day
Second dose reduction (Dose level -2)	75mg/day*
If further dose reduction below 75mg/day is required, discontinue treatment	

Haematological:

Table 2: Dose modification of palbociclib and management-Haematological toxicities

ANC (x10^9/L)	Platelets (x 10^9/L)	Dose Modifications
≥ 1.0	≥ 50	No dose adjustment is required.
0.5-0.99	25-49	Day 1 of cycle: Withhold palbociclib, repeat complete blood count monitoring within 1 week. When recovered to ANC ≥ 1x10^9/L and platelets≥ 50 x10^9/L, start the next cycle at the *same dose*. Day 15 of first 2 cycles: If Grade 3 (ANC 0.5- <1 x 10^9/L, platelets 25-<50 x 10^9/L)) on Day 15, continue palbociclib at the current dose to complete cycle and repeat complete blood count on Day 22. If Grade 4 (ANC < 0.5 x 10^9/L, platelets < 25 x 10^9/L) on Day 22, see Grade 4 dose modification guidelines below. Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of subsequent cycles.

0.5-0.99 + Fever ≥38.5^{0}C and/or infection	Any	Withhold palbociclib until recovery to ANC ≥ 1x10^9/L and platelets ≥ 50 x10^9/L Resume at next lower dose
<0.5	<25	Withhold palbociclib until recovery to ANC ≥ 1x10^9/L and platelets ≥ 50 x10^9/L Resume at next lower dose

*Grading according to CTCAE 4.0.

Renal and Hepatic Impairment:

Table 3: Dose modification of palbociclib in renal and hepatic impairment

Renal Impairment		Hepatic Impairment	
CrCl (ml/min)	**Dose Modifications**		**Dose Modifications**
≥ 15	No dose adjustment required	**Mild (Child Pugh Class A)**	No dose adjustment required
Patients requiring haemodialysis	Insuffucient data available to provide any dose adjustment recommendations	**Moderate (Child Pugh Class B)**	
		Severe (Child Pugh Class C)	75mg

Non-Haematological Toxicity:

Table 4: Palbociclib dose modification and management- Non Haematological toxicities

CTCAE Grade*	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade ≥ 3 non-haematological toxicity (if persisting despite medical treatment)	Withhold palbociclib until symptoms resolve to: • Grade ≤ 1, • Grade 2 (if not considered a safety risk for the patient) Resume at the next lower dose

*Grading according to CTCAE 4.0.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to Low (**Refer to local policy).**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

- Ovarian ablation or suppression with an LHRH agonist is mandatory when pre/perimenopausal women are administered palbociclib in combination with an aromatase inhibitor, due to the mechanism of action of aromatase inhibitors.
- Palbociclib in combination with fulvestrant in pre/perimenopausal women has only been studied in combination with an LHRH agonist.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.
Palbociclib is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Infections:** Patients should be monitored for signs and symptoms of infection and treated as medically appropriate.
- **Interstitial lung disease (ILD) and/or pneumonitis:** Patients should be regularly monitored for pulmonary symptoms indicative of ILD and/or pneumonitis. Patients with new or worsening respiratory symptoms should have treatment interrupted for further evaluation. Patients found to have severe ILD or pneumonitis should have CDK 4/6 inhibitor therapy permanently discontinued.
- **Concomitant treatment with inhibitors or inducers of CYP3A4:** Strong inhibitors of CYP3A4 may lead to increased toxicity. Concomitant use of strong CYP3A inhibitors during treatment with palbociclib should be avoided. Co-administration should only be considered after careful evaluation of the potential benefits and risks. If co-administration with a strong CYP3A inhibitor is unavoidable, reduce the palbociclib dose to 75 mg once daily. When the strong inhibitor is discontinued, increase the palbociclib dose (after 3–5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor.
  Coadministration of CYP3A inducers may lead to decreased palbociclib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of palbociclib with strong CYP3A4 inducers should be avoided. No dose adjustments are required for coadministration of palbociclib with moderate CYP3A inducers.
- **Women of childbearing potential or their partners:** Women of childbearing potential or their male partners must use a highly effective method of contraception while taking palbociclib.

DRUG INTERACTIONS:

- The concomitant use of strong CYP3A4 inhibitors or strong CYP3A4 inducers and palbociclib should be avoided.
- The dose of sensitive CYP3A substrates with a narrow therapeutic index may need to be reduced when coadministered with palbociclib as palbociclib may increase their exposure.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Palbociclib - L01XE33

REFERENCES:

1. Finn RS, Martin M et al. Palbociclib and Letrozole in Advanced Breast Cancer NEJM 2016 ;375:1925-36.
2. Cristofannilli 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 2016;17 (4):425-439
3. IBRANCE® Summary of Product Characteristics Accessed October 2020. Available at https://www.ema.europa.eu/en/documents/product-information/ibrance-epar-product-information_en.pdf
4. FDA Special Alerts: Cyclin-Dependent Kinase 4/6 Inhibitors Safety Alert September 2019 available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-severe-lung-inflammation-ibrance-kisqali-and-verzenio-breast-cancer

Version	Date	Amendment	Approved By
1	31/05/2018		Dr J Walshe
2	18/10/2018	Updated Regular Tests	Dr J Walshe
3	23/10/2019	Updated adverse events/regimen specific complications as per FDA Safety alert regarding ILD/pneumonitis	Prof Maccon Keane
4	23/10/2020	Reviewed. Updated regular tests section.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.