Indication	First line endocrine therapy for oestrogen receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. NB: Previous hormone therapy with anastrozole or letrozole whether 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. NB: No prior treatment with a CDK 4/6 inhibitor unless either ribociclib has had to be stopped within 3 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression or palbociclib has been received as part of the compassionate use scheme and the patient meets all the other commissioning criteria
Treatment Intent	Palliative
Frequency and number of cycles	Every 28 days Until disease progression or excessive toxicity or patient choice to discontinue.
Monitoring parameters pre-treatment	• Monitor FBC at baseline then at the beginning of each cycle. On cycles 1 & 2 monitor FBC on Day 15. • At the start of each cycle ensure Neuts >/= 1 and Plt >/=50. • Monitor U&E and LFT at each cycle. • The most common Grade ≥3 adverse reactions of palbociclib were neutropenia, leukopenia, anaemia, fatigue, and infections. • If patient is pre or peri-menopausal they must have undergone ovarian ablation or suppression with LHRH agonist treatment • Dose Modifications of palbociclib: First dose reduction to 100mg/day, second dose reduction to 75mg/day. If further dose reduction required, discontinue treatment • Haematological toxicities, see table 1. Non-haematological toxicities, see table 2. • Hepatic impairment: No dose adjustment required for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose is 75 mg once daily for 21 consecutive days followed by 7 days off treatment. • Renal impairment: No dose adjustment is required for patients with mild, moderate or severe renal impairment (CrCl ≥15 mL/min). Insufficient data are available in patients requiring haemodialysis to provide any dose adjustment recommendation. • Drug interactions: Avoid concomitant use of palbociclib with strong CYP3A inhibitors (eg ketoconazole, itraconazole, clarithromycin) and consider an alternative medication with no or minimal CYP3A inhibition. If patients must be co-administered a strong CYP3A inhibitor, reduce palbociclib dose to 75mg/day If 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. Concomitant use of palbociclib with strong CYP3A4 inducers (carbamazepine, phenytoin, rifampicin) should be avoided as it may lead to reduced palbociclib exposure. Use with St Johns Wort is contraindicated Caution with CYP3A substrates with a narrow therapeutic index (e.g.cyclosporine, fentanyl, tacrolimus); the dose may need to be reduced as palbociclib may increase their exposure.
Reference(s)	SpC accessed on line 16/05/18

NB For funding information, refer to the SACT funding spread sheet

Table 1: Haematological Toxicities (Table applies to all haematological adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).

CTCAE Grade	Dose modifications of palbociclib
Grade 1 or 2	No dose adjustment is required.
Grade 3 e.g Neuts 0.5 - <1.0 PLT 25 - <50	Day 1 of cycle: Withhold palbociclib repeat complete blood count monitoring within 1 week. When recovered to Grade ≤2, start the next cycle at the *same dose*. Day 15 of first 2 cycles: If Grade 3 on Day 15, continue at the *current dose* to complete cycle and repeat complete blood count on Day 22. 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.
Grade 3 neutropenia (Neuts 0.5 - <1.0)+ Fever ≥38.5 °C and/or infection	Withhold palbociclib until recovery to Grade ≤2 Resume at next lower dose.
Grade 4 e.g neuts <0.5 PLT <25	At any time: Withhold palbociclib until recovery to Grade ≤2. Resume at next lower dose.

Table 2 Non-haematological toxicities

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

Repeat every 28 days

TTO	Drug	Dose	Route	Directions
1	Palbociclib	125mg	PO	Once DAILY for 21 days followed by a 7 day break Swallow whole, do not chew, crush or open capsules. Take the dose at approximately the same time each day with food, preferably a meal. If a dose is missed or vomiting occurs, an additional dose should not be taken that day. Do not take with pomegranate, seville orange, grapefruit or grapefruit juice. Available as 125mg, 100mg or 75mg capsules.
	Letrozole	2.5mg	PO	Once DAILY