Abemaciclib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Abemaciclib in combination with endocrine therapy for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence.	C50	00619a	CDS 01/06/2024

* This is for post 2012 indications only

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.

Abemaciclib is administered orally twice daily in combination with endocrine therapy, treatment should be taken continuously for two years or until disease progression or unacceptable toxicity occurs.

In pre- or perimenopausal women, aromatase inhibitor endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

Drug	Dose	Route and Method of administration	Cycle
Abemaciclib	150 mg twice daily	PO with or without food	Continuous for 2 years
Treatment doses should be taken at approximately the same times each day. Swallow whole, do not chew, split or crush. Abemaciclib should not be taken with grapefruit or grapefruit juice. If a patient vomits or misses a dose of abemaciclib, the patient should be instructed to take the next dose at its scheduled time; an additional dose should not be taken.			

ELIGIBILITY:

- Indication as above
- Patient has undergone definitive surgery of primary breast tumour
- Breast Cancer at High risk of recurrence defined as patients with either:
  - 4+ positive axillary lymph nodes OR
  - 1-3 positive axillary lymph nodes and a primary tumour size greater than or equal to 5 cm and/or histological Grade 3 disease
- ECOG 0-1
- Adjuvant abemaciclib should start within 16 months of tumour resection
- Patient may receive up to 12 weeks of endocrine therapy prior to commencing adjuvant abemaciclib following the last non-endocrine therapy (surgery, chemotherapy, or radiation) whichever is last
- Adequate organ function

CAUTIONS:

- Previous history of venous thromboembolic event (VTE)

EXCLUSIONS:

- Hypersensitivity to abemaciclib or any of the excipients.
- Metastatic disease, node negative breast cancer, inflammatory breast cancer
- Previous treatment with CDK4 or CDK6 inhibitors
- 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, renal and liver profile every two weeks for the first two months, then monthly for the next two months and then as clinically indicated

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 dose interruption and/or dose reduction as outlined in Tables 2-8

Table 1: Dose reduction levels for adverse reactions

Dose level	Abemaciclib Dose
Recommended Dose	150mg twice daily
First dose reduction	100mg twice daily
Second dose reduction	50mg twice daily

Haematological:

Prior to treatment initiation ANC ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L and Hb≥8g/dL are recommended.

Table 2: Dose modification of abemaciclib in haematological toxicity

Toxicity[a, b]	Management recommendations
Grade 1 or 2	No adjustment required
Grade 3	Suspend dose until toxicity to Grade ≤2. Dose reduction is not required.
Grade 3 recurrent or Grade 4	Suspend dose until toxicity to Grade ≤2. Resume at next lower dose.
Patient requires administration of blood cell growth factors	Suspend dose for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to Grade ≤2. Resume at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.

[a] NCI Common Terminology Criteria for Adverse Events (CTCAE)
Grade 1: ANC > 1.5 x 10^9/L
Grade 2: ANC 1.0 - 1.5 x 10^9/L
Grade 3: ANC 0.5 – 1.0 x 10^9/L
Grade 4: ANC < 0.5 x 10^9/L

Renal and Hepatic Impairment:

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

Renal Impairment		Hepatic Impairment	
CrCl (ml/min)	**Dose**		**Dose**
≥30	No dose adjustment is needed	Child-Pugh A/B:	No dose adjustment is needed
<30	No need for dose adjustment is expected	Child-Pugh C	Reduce dose frequency to once daily
Haemodialysis	No need for dose adjustment is expected		

Management of adverse events:

Table 4: Dose Modification for management of diarrhoea

Toxicity Grade*	Recommended dose modification
Grade 1	No dose adjustment required.
Grade 2	If toxicity does not resolve within 24 hours to Grade ≤1, suspend dose until resolution. Dose reduction is not required
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to Grade ≤1. Resume at next lower dose.
Grade 3 or 4 or requires hospitalisation	

* NCI Common Terminology Criteria for Adverse Events (CTCAE)

Table 5: Dose Modification for management of increased aminotransferases

Toxicity Grade*	Recommended dose modification
Grade 1 (>ULN-3.0 x ULN) **Grade 2** (3.0-5.0 x ULN)	No dose adjustment required.
Persistent or Recurrent **Grade 2 or Grade 3** (>5.0-20.0 x ULN)	Suspend dose until toxicity resolves to baseline or Grade 1 Resume at next lower dose.
Elevation in AST and/or ALT >3 x ULN **WITH** total bilirubin >2 x ULN, in the absence of cholestasis	Discontinue abemaciclib
Grade 4 (>20.0 x ULN)	Discontinue abemaciclib

* NCI Common Terminology Criteria for Adverse Events (CTCAE)

Table 6: Dose Modification for management of interstitial lung disease (ILD)/pneumonitis

Toxicity Grade*	Recommended dose modification
Grade 1 or 2	No dose adjustment required.
Persistent or recurrent **Grade 2** toxicity that does not resolve with maximal supportive measures within 7 days to baseline or **Grade 1**	Suspend dose until toxicity resolves to baseline or Grade 1 Resume at next lower dose.
Grade 3 or 4	Discontinue abemaciclib

* NCI Common Terminology Criteria for Adverse Events (CTCAE)

Table 7: Dose Modification for management of venous thromboembolic events (VTE's)

Toxicity Grade*	Recommended dose modification
All grades (1, 2, 3, 4)	Suspend dose and treat as clinically indicated. Abemaciclib may be resumed when the patient is clinically stable.

* NCI Common Terminology Criteria for Adverse Events (CTCAE)

Table 8: Dose Modification for management of non-haematologic toxicities

Toxicity Grade*	Recommended dose modification
Grade 1 or 2	No dose adjustment required.
Persistent or recurrent **Grade 2** toxicity that does not resolve with maximal supportive measures to baseline or Grade 1 within 7 days	Suspend dose until toxicity resolves to Grade ≤1. Resume at next lower dose.
Grade 3 or 4	

* NCI Common Terminology Criteria for Adverse Events (CTCAE)

Concomitant treatment with inhibitors of CYP3A4:

Strong inhibitors of CYP3A4 may lead to increased toxicity. Concomitant use of strong CYP3A inhibitors during treatment with abemaciclib should be avoided.

- If co-administration with a strong CYP3A inhibitor is unavoidable, reduce the abemaciclib dose to 100mg twice daily

- In patients who have had their dose reduced to 100mg abemaciclib twice daily and in whom co-administration of a strong CYP3A4 inhibitor cannot be avoided, the dose should be further reduced to 50mg twice daily
- In patients who have had their dose reduced to 50mg abemaciclib twice daily and in whom the co-administration of a strong CYP3A4 inhibitor cannot be avoided, the abemaciclib dose may be continued with close monitoring of signs of toxicity. Alternatively, the abemaciclib dose may be reduced to 50mg once daily or discontinued
- If the CYP3A4 inhibitor is discontinued, the abemaciclib dose should be increased to the dose used prior to the initiation of the CYP3A4 inhibitor (after 3 to 5 half-lives of the CYP3A4 inhibitor)

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL

- As outlined in NCCP Classification Document for Systemic Anti Cancer Therapy (SACT) Induced Nausea and Vomiting linked here

Abemaciclib Moderate to high (**Refer to local policy).**

For information:
Within NCIS regimens, anti-emetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following document:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link here
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - link here

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

Treatment with anti-diarrhoeal agents, such as loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see local policy) should be started at the first sign of loose stools.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Infections:** infections were reported in patients receiving abemaciclib plus endocrine therapy. Patients should be monitored for signs and symptoms of infection and treated as medically appropriate.
- **Venous thromboembolism:** Venous thromboembolic events were reported in patients treated with abemaciclib plus endocrine therapy. Patients should be monitored for signs and symptoms of deep vein thrombosis and pulmonary embolism and treated as medically appropriate.

- **Increased aminotransferases:** Increases in ALT and AST were reported in patients receiving abemaciclib. Based on the level of ALT or AST elevation, abemaciclib may require dose modification
- **Diarrhoea**: is the most common adverse reaction. Patients should start treatment with anti-diarrhoeal agents such as loperamide at the first sign of loose stools, increase oral fluids and notify their healthcare provider. Dose modification is recommended for patients who develop ≥ Grade 2 diarrhoea as described in table 4.
- **Interstitial lung disease (ILD) and/or pneumonitis** was reported in patients receiving abemaciclib. Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis and treat as medically appropriate. Based on the grade of ILD/pneumonitis, abemaciclib may require dose modification. Permanently discontinue abemaciclib in patients with Grade 3 or 4 ILD/pneumonitis, as per table 6.
- **Concomitant use of inducers of CYP 3A4:** Concomitant use of CYP3A4 inducers should be avoided due to the risk of decreased efficacy of abemaciclib
- **Women of childbearing potential:** Women of childbearing potential should use a highly effective method of contraception (e.g. double-barrier contraception) while taking abemaciclib and for at least 3 weeks after completing therapy.

DRUG INTERACTIONS:

- The concomitant use of strong CYP3A4 inhibitors or strong CYP3A4 inducers and abemaciclib should be avoided - see dose modification for further details
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Johnson SRD et al. Abemaciclib Combined with Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node+, High-risk, Early Breast Cancer (monarchE). J Clin Oncol 2020. Dec 1;38(34):3987-3998
2. Giraud EL, de Lijster B, Krens SD, Desar IME, Boerrigter E, van Erp NP. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Lancet Oncol 2023; 24: e229. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
4. Abemaciclib (Verzenios®) Summary of Product Characteristics. Accessed March 2024. Available at https://www.ema.europa.eu/en/documents/product-information/verzenios-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	31/05/2024		Prof Michaela Higgins
2	08/07/2024	Updated caution section	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.