Abemaciclib (Verzenios®) in combination with endocrine therapy for the adjuvant treatment of early breast cancer

General information

Drug description [1]	Indication [2]
Abemaciclib (Verzenios®) is an oral, continuously dosed, cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor.	Abemaciclib (Verzenios®) in combination with endocrine therapy is indicated 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.

Current treatment [3]

The following treatments are recommended in the early phase of breast cancer:

- Chemotherapy
  - Examples of chemotherapy for early breast cancer include docetaxel – cyclophosphamide, epiribicin – cyclophosphamide, doxorubicin – cyclophosphamide, paclitaxel, and cyclophosphamide – methotrexate – fluorouracil
- Bisphosphonate therapy
  - Zoledronic acid or sodium clodronate as adjuvant therapy for postmenopausal women to reduce the risk of cancer spreading to other areas of the body
- Hormone therapy
  - Tamoxifen as a treatment for oestrogen receptor-positive breast cancer
  - Aromatase inhibitors, such as anastrozole, exemestane and letrozole for postmenopausal women with oestrogen receptor-positive breast cancer

Regulatory status

EMA [2]

Approval status for this indication: On 24 February 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Verzenios®.

The CHMP adopted an extension to the existing indication:

- Verzenios® in combination with endocrine therapy is indicated for the adjuvant treatment of adult patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence. In pre- or perimenopausal women, aromatase inhibitor endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

✓ **Medicine under additional monitoring**

Other indications:

- Verzenios® is indicated for the treatment of women with HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy. In pre- or perimenopausal women, the endocrine therapy should be combined with a LHRH agonist.

FDA [4, 5]

Approval status for this indication: On 12 October 2021, the FDA approved abemaciclib (Verzenio®) with endocrine therapy (tamoxifen or an aromatase inhibitor) for adjuvant treatment of adult patients with HR-positive, HER2-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20%, as determined by an FDA approved test.

- ✓ This is the first CDK 4/6 inhibitor approved for adjuvant treatment of breast cancer.
- ✓ FDA also approved the Ki-67 IHC MIB-1 pharmDx (Dako Omnis) assay as a companion diagnostic for selecting patients for this indication.

Other indications: Verzenio® is indicated:

- in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women and men, with HR-positive, HER2-negative advanced or metastatic breast cancer.
- in combination with fulvestrant for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.
- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

Costs [6]

56 Verzenios® tablets 150 mg = € 2,618.50 (ex-factory price)

Warnings and precautions [4]

- **Diarrhoea**
  - Verzenio® can cause severe cases of diarrhoea, associated with dehydration and infection. Instruct patients at the first sign of loose stools to initiate antidiarrheal therapy, increase oral fluids, and notify their healthcare provider.
- **Neutropenia**
  - Monitor complete blood counts prior to the start of Verzenio® therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.
- **Interstitial lung disease (ILD)/pneumonitis**
  - Severe and fatal cases of ILD/pneumonitis have been reported. Monitor for clinical symptoms or radiological changes indicative of ILD/pneumonitis. Permanently discontinue Verzenio® in all patients with Grade 3 or 4 ILD or pneumonitis.
- **Hepatotoxicity**
  - Increases in serum transaminase levels have been observed. Perform liver function tests (LFTs) before initiating treatment with Verzenio®. Monitor LFTs every two weeks for the first two months, monthly for the next 2 months, and as clinically indicated.
- **Venous thromboembolism**
  - Monitor patients for signs and symptoms of thrombosis and pulmonary embolism and treat as medically appropriate.
- **Embryo-foetal toxicity**
  - Can cause foetal harm. Advise patients of potential risk to a foetus and to use effective contraception.

Study characteristics [1, 7]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
monarchE NCT03155997	5,637	abemaciclib 150 mg twice daily on a continuous dosing schedule + endocrine therapy	endocrine therapy alone	invasive disease-free survival (IDFS)	**ongoing**, open-label[1], global, randomised, phase 3 trial	HR+, HER2	Eli Lilly and Company	[1]

Efficacy (I vs. C), interim analysis data

At the time of the data cut-off (16 March 2020), 12.5% of patients had completed the 2-year treatment period, and 72.8% of patients were still in the 2-year treatment period.
Median follow-up time was approx. **15.5 months** in both arms.
I demonstrated a **statistically significant** improvement in **IDFS** versus C (Hazard ratio 0.75; 95% CI, 0.60-0.93; p= 0.01)
2-year IDFS rates: 92.2% vs. 88.7%
DRFS improvement in I vs. C: Hazard ratio 0.72; 95% CI, 0.56-0.92; nominal p= 0.01
2-year DRFS rates: 93.6% vs. 90.3%
OS data: immature, 1.4% vs. 1.3% deaths

Patient-reported outcomes: will be reported separately

Safety (I vs. C), interim analysis data

Treatment-emergent AEs: 97.9% vs. 86.1%
Venous thromboembolic events: 2.3% vs. 0.5%
ILD: 2.7% vs. 1.2%
Grade ≥ 3 AEs: 45.9% vs. 12.9%
SAEs: 12.3% vs. 7.2%
Discontinuation of abemaciclib due to AEs: 16.6%
Discontinuation of both treatments due to AEs: 6.2%
Discontinuations in the control arm: 0.8%
Deaths on study treatment or within 30 days of discontinuation[2]: 0.5% vs. 0.5%

[1] Although this was an open-label study, the sponsor and all investigative sites remained blinded to treatment group assignments for aggregate data until the study was confirmed as positive.
[2] In the abemaciclib arm, 11 were due to AEs (two, diarrhea and pneumonitis, considered possibly related to study treatment by the investigator) versus seven as a result of AEs in the control arm.

ESMO-MCBS version 1.1 [8]											
Scale	Int.	Form	MG ST	MG	Hazard ratio (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	Adjuvant	1	-	-	0.75 (0.60-0.93)	Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	A	-	-	-	A
Adapted	Adjuvant	1	-	-	0.75 (0.60-0.93)	Improvement in DFS alone (Hazard ratio 0.65-0.8) without mature survival data	B	-	-	-	B

Risk of bias (RCT) [9]					
Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	-	no, open-label	unclear[3]	yes[4]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CDK4/6=cyclin-dependent kinase 4 and 6, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, DRFS=Distant relapse–free survival, EMA=European Medicines Agency, ER=oestrogen receptor, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HER2=human epidermal growth factor receptor 2, HR=hormone receptor, I=intervention, IDFS=invasive disease-free survival, ILD=interstitial lung disease, Int.=intention, LFTs=liver function tests, LHRH=luteinising hormone-releasing hormone, MG=median gain, n=number of patients, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment

References:

1. Johnston S, Harbeck N, Hegg R, Toi M, et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). J Clin Oncol 38:3987-3998. [Available from: https://ascopubs.org/doi/10.1200/JCO.20.02514]
2. European Medicines Agency (EMA). Medicines. Verzenios. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/verzenios].
3. National Institute for Health Research (NIHR). Abemaciclib for early breast cancer – adjuvant treatment. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2020/09/23786-Abemaciclib-for-Breast-Cancer-V1.0-AUG2020-NON-CONF.pdf].
4. U.S. Food and Drug Administration (FDA). Verzenio. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208716s006s007s008lbl.pdf].
5. U.S. Food and Drug Administration (FDA). FDA approves abemaciclib with endocrine therapy for early breast cancer.
6. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
7. U.S. National Library of Medicine, ClinicalTrials.gov. Endocrine Therapy With or Without Abemaciclib (LY2835219) Following Surgery in Participants With Breast Cancer (monarchE). [Available from: https://clinicaltrials.gov/ct2/show/NCT03155997].

[3] Currently, only interim analysis data is available. The monarchE trial is ongoing; estimated study completion date is 06/2029.
[4] Industry-funded trial.

8. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28: 2340–2366, 2017.
9. European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].