Elacestrant (Orserdu®) monotherapy for the treatment of oestrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer

General information [1]

Drug description

The active substance of Orserdu® is elacestrant, an anti-oestrogen endocrine therapy. Elacestrant selectively binds to oestrogen receptor-α (ERα) and degrades ERα protein, disrupting ERα signalling and thereby inhibiting the growth of ERα-positive breast cancer cells, including those harbouring oestrogen receptor 1 (ESR1) gene mutations.

Indication

Elacestrant (Orserdu®) monotherapy is indicated for the treatment of postmenopausal women, and men, with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor.

Incidence [2]

In Austria, in 2020, 5,443 women and 87 men were newly diagnosed with breast cancer.
The age-standardised incidence rate[1] was 111.4 per 100,000 women and 2.1 per 100,000 men.

Current treatment

Adjuvant endocrine therapy in postmenopausal women [3]:

- For the adjuvant endocrine systemic therapy in postmenopausal women with ER-positive breast cancer, tamoxifen and aromatase-inhibitors are available.
- Tamoxifen administration ≥5 years led to a significant decrease in cancer-specific mortality of 30% and overall mortality of 22%, as compared with patients without adjuvant systemic therapy (according to a meta-analysis of the Early Breast Cancer Trialists' Collaborative Group).
- Aromatase inhibitors, administered as upfront therapy, led to a significant decrease of the relapse risk throughout the first 2 years after beginning of treatment; letrozole approval study as well as a meta-analysis showed a decrease of mortality by aromatase inhibitors.
- In high-risk patients (e.g., N+), adjuvant therapy with an aromatase inhibitor is recommended; whether as monotherapy or as sequential therapy with switch over to tamoxifen.
- In switch-trials, aromatase inhibitors - administered after tamoxifen – decreased the breast cancer-specific mortality.

Primary (neoadjuvant) therapy in locally advanced breast cancer in men [4]:

- In locally advanced breast cancer (stages IIIA and IIIB), primary therapy (neoadjuvant, preoperative) with administration of anthracyclines and taxanes for a treatment duration of ≥18 weeks is possible.
- Primary endocrine therapy with tamoxifen provides an option for patients with ER-positive tumours if surgery or chemotherapy are contraindicated or are denied.
- Primary systemic therapy is part of a multimodal treatment concept and gets continued with surgery, radiation therapy and systemic endocrine therapy, considering the indications of localised breast cancer.

Regulatory status

EMA [1]	FDA [5]
Approval status for this indication: On 20 July 2023, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Orserdu®. UPDATE: Marketing authorisation issued on15/09/2023 [6]. The full indication is: ❖ Orserdu® monotherapy is indicated for the treatment of postmenopausal women, and men, with ER-positive, HER2-negative, locally advanced, or metastatic breast cancer with an activating ESR1	**Approval status for this indication**: On 27 January 2023, the FDA approved elacestrant (Orserdu®) for postmenopausal women or adult men with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy. FDA also approved the Guardant360 CDx assay as a companion diagnostic device to identify patients with breast cancer for treatment with elacestrant. **Other indications**: none

[1] European Standard Population 2013.

mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor.

- ❖ Orserdu is available as 86 mg and 345 mg film-coated tablets.

Other indications: none

- ✓ Medicine is under additional monitoring
- ✓ Orphan medicine

Manufacturer

Orserdu® is manufactured by Stemline Therapeutics B.V.

Costs [7]

28 Orserdu® film tablets 86 mg = € 3,047.80 (ex-factory price)
28 Orserdu® film tablets 345 mg = € 8,500.00 (ex-factory price)

Posology [8]

- ❖ Treatment with Orserdu® should be initiated by a physician experienced in the use of anticancer therapies.
- ❖ Patients with ER-positive, HER2-negative advanced breast cancer should be selected for treatment with Orserdu® based on the presence of an activating ESR1 mutation in plasma specimens, using a CE marked in vitro diagnostic (IVD) with the corresponding intended purpose. If the CE-marked IVD is not available, the presence of an activating ESR1 mutation in plasma specimens should be assessed by an alternative validated test.
- ❖ The recommended dose is 345 mg (one 345 mg film-coated tablet), once daily.
- ❖ The maximum recommended daily dose of Orserdu® is 345 mg.
- ❖ Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Warnings and precautions [8, 9]

- ❖ **Dyslipidaemia**
  - Orserdu® may cause hypercholesterolemia and hypertriglyceridemia.
  - Monitor lipid profile prior to starting treatment and periodically thereafter.
- ❖ **Embryo-foetal toxicity**
  - Orserdu® can cause foetal harm.
  - Advise of the potential risk to a foetus and to use effective contraception.
- ❖ **Hepatic impairment**
  - Orserdu® is metabolised by the liver, and impaired hepatic function can increase the risk for adverse reactions.
  - Therefore, Orserdu® should be used cautiously in patients with hepatic impairment and patients should be regularly and closely monitored for adverse reactions.
  - Administration of elacestrant should be undertaken with caution at a dose of 258 mg once daily in patients with moderate hepatic impairment.
  - In the absence of clinical data, elacestrant is not recommended in patients with severe hepatic impairment (Child-Pugh C).
- ❖ **Concomitant use with CYP3A4 inhibitors**
  - Concomitant administration of Orserdu® with strong CYP3A4 inhibitors including, but not limited to: clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole, and grapefruit or grapefruit juice should be avoided. An alternative concomitant medicinal product with no or minimal potential to inhibit CYP3A4 should be considered. If the strong CYP3A4 inhibitor cannot be avoided, Orserdu® dose adjustment should be applied.

- Concomitant administration of Orserdu® with moderate CYP3A4 inhibitors including, but not limited to: aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, grapefruit juice, imatinib, isavuconazole, tofisopam and verapamil should be avoided. An alternative concomitant medicinal product with no or minimal potential to inhibit CYP3A4 should be considered. If the moderate CYP3A4 inhibitor cannot be avoided, Orserdu® dose adjustment should be applied.

❖ **Concomitant use with CYP3A4 inducers**

- Concomitant administration of Orserdu® with strong CYP3A4 inducers including, but not limited to: phenytoin, rifampicin, carbamazepine and St John's Wort (Hypericum perforatum) should be avoided. An alternative concomitant medicinal product with no or minimal potential to induce CYP3A4 should be considered. If the strong CYP3A4 inducer cannot be avoided, Orserdu® dose adjustment should be applied.
- Concomitant administration of Orserdu® with moderate CYP3A4 inducers including, but not limited to: bosentan, cenobamate, dabrafenib, efavirenz, etravirine, lorlatinib, phenobarbital, primidone and sotorasib should be avoided. An alternative concomitant medicinal product with no or minimal potential to induce CYP3A4 should be considered. If the moderate CYP3A4 inducer cannot be avoided, Orserdu® dose adjustment should be applied.

❖ **Thromboembolic events**

- Thromboembolic events are commonly observed in patients with advanced breast cancer and have been observed in clinical studies with Orserdu®.
- This should be taken into consideration when prescribing Orserdu® to patients at risk.

Study characteristics [10, 11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
EMERALD, RAD1901-308 NCT03778931	477 (1:1)	elacestrant 400 mg orally once daily	SOC endocrine monotherapy[2]	PFS by BICR in all patients and patients with detectable ESR1 mutations	15.1 months	**ongoing[3],** international, multicentre, randomised, open-label, phase III trial	ESR1	Radius Health, Inc.	EMERALD trial [10]

Inclusion criteria [4]

- ❖ Postmenopausal women or men ≥18 years with histologically or cytologically proven ER-positive/HER2-negative breast adenocarcinoma and either locoregionally recurrent or metastatic disease.
- ❖ Disease progression must have occurred during or within 28 days after treatment with one or two prior lines of endocrine therapy for advanced/metastatic disease.
- ❖ Progression during or within 12 months of adjuvant endocrine therapy was included as a line of endocrine therapy for advanced/metastatic disease.
- ❖ Progression on previous CDK4/6 inhibitor treatment in combination with fulvestrant or an AI was required.
- ❖ One chemotherapy regimen in the advanced/metastatic setting was permitted.
- ❖ ECOG PS 0 or 1.
- ❖ Measurable disease per RECIST version 1.1 or evaluable bone-only disease with at least one lytic or mixed lyticblastic bone lesion (blastic-only metastases were not allowed).

Exclusion criteria

- ❖ Symptomatic metastatic visceral disease and any of the following cardiovascular events within 6 months of enrolment:
  - severe/unstable angina,
  - myocardial infarction,
  - coronary/peripheral artery bypass graft,
  - prolonged corrected QT interval grade ≥2,
  - uncontrolled atrial fibrillation, ongoing grade ≥2 cardiac dysrhythmias,
  - New York Heart Association Class II or greater heart failure,
  - coagulopathy (thrombosis),
  - cerebrovascular accident.

Patient characteristics at baseline (I vs. C)

- ❖ Median age: 63 vs. 64 years
- ❖ Female sex: 97.5% vs. 99.6%
- ❖ ECOG PS 0: 59.8% vs. 56.7%
- ❖ Visceral metastasis: 68.2% vs. 71.0%
- ❖ Prior adjuvant therapy: 66.1% vs. 59.2%
- ❖ Prior CDK4/6 inhibitor: 100% vs. 100%
- ❖ No. of prior lines of endocrine therapy in the advanced or metastatic setting:
  - 1: 54.0% vs. 59.2%
  - 2: 46.0% vs. 40.8%
- ❖ No. of prior lines of chemotherapy in the advanced or metastatic setting:
  - 0: 79.9% vs. 75.6%
  - 1: 20.1% vs. 24.4%
- ❖ Prior therapies for advanced or metastatic disease:
  - Any prior endocrine therapy: 97.1% vs. 97.7%
    - o Fulvestrant: 29.3% vs. 31.5%
    - o AI: 80.8% vs. 81.1%

[2] SOC treatment was per investigator's choice of fulvestrant, anastrozole, letrozole, or exemestane monotherapy and dosed according to the labelling.
[3] Estimated study completion date is 08/2024.
[4] For detailed in- and exclusion criteria, please see study protocol.

❖ ER and HER2 testing were performed by local laboratory. ER positivity was defined as ≥1% staining by immunohistochemistry, with or without progesterone receptor positivity. HER2 negativity was defined according to current guidelines.		o Tamoxifen: 7.9% vs. 6.3% • mTOR inhibitor: 4.2% vs. 2.5% • PI3K inhibitor: 1.1% vs. 0.4%

Efficacy (I vs. C)	**Safety** (I vs. C)
<u>Primary analysis, data cutoff 6 September 2021; median duration of follow up 15.1 months:</u> **PFS by BICR**: statistically significantly prolonged HR 0.70 (95% CI, 0.55-0.88; p= .002, all patients); HR 0.55 (95% CI, 0.39-0.77, p= 0.0005; patients with ESR1 mutation) **6-month PFS rates in all patients**: 34.3% (95% CI, 27.2-41.5) vs. 20.4% (95% CI, 14.1-26.7) **6-month PFS rates in patients with ESR1 mutation**: 40.8% (95% CI, 30.1-51.4) vs. 19.1% (95% CI, 10.5-27.8) **12-month PFS rates in all patients**: 22.3% (95% CI, 15.2-29.4) vs. 9.4% (95% CI, 4.0-14.8) **12-month PFS rates in patients with ESR1 mutation**: 26.8% (95% CI, 16.2-37.4) vs. 8.2% (95% CI, 1.3-15.1) **<u>Efficacy of elacestrant compared with the fulvestrant subgroup in secondary analysis:</u>** Results remained significant in favour of elacestrant, both in the overall population or **ESR1 mutation cohort**, in terms of statistical significance (p= 0.0019; **0.0006**); **estimates of median PFS** (2.8 months vs. 1.9 months; **3.8 months vs. 1.9 months**) **6-month PFS rate**: 34.3% vs. 20.6%; 40.8% vs. 19.3%) **12-month PFS rate:** 22.3% vs. 9.5%; 26.8% vs. 8.3%) **<u>Interim analysis of OS:</u>** **Events in all patients**: 149; HR 0.75 (95% CI, 0.54-1.04; p = 0.08) **Events in patients with ESR1 mutation:** 68 events; HR 0.59 (95% CI, 0.36-0.96; p = 0.03, nonsignificant) **Events in patients without ESR1 mutation**: 81; HR 0.92 (95% CI, 0.59-1.42; p= 0.69)	**AEs:** 92.0% vs. 86.0% **AEs grade 3-4:** 27.0% vs. 20.5% **AEs leading to treatment discontinuation:** 6.3% vs. 4.4% **Events deemed treatment-related by the investigator:** 63.3% vs. 43.7% **Events of grade 3-4 deemed treatment-related by the investigator:** 7.2% vs. 3.1%

Patient-reported outcomes

The assessment of patient-reported outcomes is not provided in EMERALD trial.

ESMO-MCBS version 1.1 [12]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2b	≤6 months	PFS: +1.9 months	HR 0.55 (0.39-0.77)	HR ≤0.65 AND gain ≥ 1.5 months	3	-	NA	+1[5]	4
Adapted	NC	2b	≤6 months	PFS: +1.9 months	HR 0.55 (0.39-0.77)	HR ≤0.65 AND gain ≥ 1.5 months	3	-	NA	+1[6]	4

Risk of bias (RCT) [13]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**

[5] >10% gain improvement in PFS in 12 months.
[6] >10% gain improvement in PFS in 12 months.

yes low risk	-	no high risk	unclear[7] unclear risk	yes[8] high risk	unclear

Ongoing trials [14]		
NCT number/trial name	Description	Estimated study completion date
NCT03778931/ EMERALD	Please see above.	08/2024
NCT05512364	An international, multi-centre, randomised, open label, superiority phase III trial of elacestrant vs. standard endocrine therapy in patients with ER+/HER2- breast cancer and ctDNA relapse.	05/2030

Available assessments

- In November 2022, NIHR published a Health Technology Briefing "Elacestrant for treating HER2-negative, ER-positive, advanced breast cancer after endocrine therapy" [15].
- No further assessment was identified via ICER; CADTH and G-BA.

Other aspects and conclusions

- In July 2023, the **CHMP adopted a positive opinion**, recommending the granting of a marketing authorisation for **Orserdu®** as monotherapy for the treatment of postmenopausal women, and men, with ER-positive, HER2-negative, locally advanced, or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK 4/6 inhibitor. Marketing authorisation was issued by the EMA on 15 September 2023. In January 2023, Orserdu® was **approved by the FDA** for this indication.
- **EMERALD (NCT03778931)** is an **ongoing**, randomised, open-label, phase III clinical study comparing the efficacy and safety of elacestrant compared with SOC endocrine therapy in patients with ER-positive/HER2-negative advanced or metastatic breast cancer who had progression after first- or second-line treatment with the combination of endocrine therapy and a CDK4/6 inhibitor and to compare efficacy between arms in patients with detectable ESR1 mutation. Included were postmenopausal women or men ≥18 years with histologically or cytologically proven ER-positive/HER2-negative breast adenocarcinoma and either locoregionally recurrent or metastatic disease and an ECOG PS of 0 or 1. Patients with symptomatic metastatic visceral disease and various cardiovascular events (ee.g., severe/unstable angina, myocardial infarction) were excluded from the trial.
- **PFS by BICR** in **all patients** and patients with **detectable ESR1** mutations is the primary endpoint of the EMERALD trial. Estimates of median PFS were 2.8 months vs. 1.9 months (HR 0.70; 95% CI, 0.55-0.88; p= 0.002) in all patients and 3.8 months vs. 1.9 months (HR 0.55; 95% CI, 0.39-0.77, p= 0.0005) in patients with ESR1 mutation, showing a **statistically significant** improvement.
- The evaluation of **patient-reported outcomes is not provided** in the EMERALD trial.
- The original and adapted **ESMO-MCBS** were applied, resulting in a final adjusted magnitude of benefit **grade 4** each.
- Since there is **no final analysis data** available, the **risk of bias** of the EMERALD trial was **considered unclear**. However, the risk is **increased** by the industry-funded background of the trial.
- Beside the EMERALD trial, one further phase 3 trial, assessing the superiority of elacestrant vs. standard endocrine therapy in patients with ER+/HER2- breast cancer and ctDNA relapse was identified.
- In conclusion, **final analysis data** from the EMERALD trial, as well as **long term data** is required. Furthermore, evaluation of **patient-reported outcomes** is essential.

First published: 08/2023
Last updated: 12/2023

Abbreviations: AE=adverse event, AI=aromatase inhibitor, AJ=adjustment, BICR=blinded independent central review, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CDK4/6=cyclin-dependent kinase, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, ctDNA=circulating tumour deoxyribonucleic acid, EMA=European Medicines Agency, ER=estrogen-receptor, ERα=oestrogen receptor-α, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, ESR1=estrogen receptor 1, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HER2=human epidermal growth factor receptor 2, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, IVD=in vitro diagnostic, MG=median gain, mTOR=mammalian

[7] The EMERALD trial is currently ongoing; final analysis data is not (yet) available.
[8] The trial was designed by a steering committee of independent investigators and the sponsor. Members of the steering committee guided the initial manuscript draft after an agreement to publish with all coauthors, with editorial assistance from professional medical writers funded by the sponsor.

target of rapamycin, n=number of patients, NICE=National Institute for Health Care Excellence, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PI3K=phosphoinositide 3-kinase, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, SOC=standard of care, ST=standard treatment

References:

1. European Medicines Agency (EMA). Medicines. Orserdu. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/orserdu].
2. Statistik Austria. Krebserkrankungen. Ausgewählte Krebslokalisationen nach Inzidenz. [Available from: https://www.statistik.at/statistiken/bevoelkerung-und-soziales/gesundheit/krebserkrankungen].
3. Onkopedia, Wörmann B, et al. Mammakarzinom der Frau. [Available from: https://www.onkopedia.com/de/onkopedia/guidelines/mammakarzinom-der-frau/@@guideline/html/index.html#ID0ENPAG].
4. Onkopedia, Wörmann B, et al. Mammakarzinom des Mannes. [Available from: https://www.onkopedia.com/de/onkopedia/guidelines/mammakarzinom-des-mannes/@@guideline/html/index.html].
5. U.S. Food and Drug Administration (FDA). FDA approves elacestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-elacestrant-er-positive-her2-negative-esr1-mutated-advanced-or-metastatic-breast-cancer].
6. European Medicines Agency (EMA). Medicines. EPAR. Orserdu. [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/orserdu].
7. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
8. European Medicines Agency (EMA). Orserdu: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/orserdu-epar-product-information_en.pdf].
9. U.S. Food and Drug Administration (FDA). Orserdu. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217639Orig1s000correctedlbl.pdf].
10. Bidard F, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. J Clin Oncol 40:3246-3256.
11. U.S. National Library of Medicine, ClinicalTrials.gov. Phase 3 Trial of Elacestrant vs. Standard of Care for the Treatment of Patients With ER+/HER2- Advanced Breast Cancer (EMERALD). [Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03778931].
12. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28: 2340–2366, 2017.
13. 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].
14. U.S. National Library of Medicine, ClinicalTrials.gov. [Available from: https://classic.clinicaltrials.gov/ct2/home].
15. National Institute for Health Research (NIHR). Elacestrant for treating HER2-negative, ER-positive, advanced breast cancer after endocrine therapy. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2023/02/27136-Elacestrant-for-Breast-Cancer-V1.0-NOV2022-NONCONF.pdf].