swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Orserdu

International non-proprietary name: elacestrant as elacestrant dihydrochloride

Pharmaceutical form: film-coated tablets

Dosage strength(s): 86 mg, 345 mg

Route(s) of administration: oral use

Marketing authorisation holder: Stemline Therapeutics Switzerland GmbH

Marketing authorisation no.: 69417

Decision and decision date: approved on 04.06.2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
BC	Breast cancer
BIRC	Blinded imaging review committee
CDK4/6	Cylin-dependent kinase 4/6
CI	Confidence interval
ctDNA	Circulating tumour DNA
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ER	Estrogen receptor
ERA	Environmental risk assessment
ESMO	European Society for Medical Oncology
ESR1	Estrogen receptor 1 gene
ET	Endocrine treatment
FDA	Food and Drug Administration (USA)
HER2	Human epidermal growth factor receptor 2
HPLC	High-performance liquid chromatography
HR	Hormone receptor
ICH	International Council for Harmonisation
INN	International non-proprietary name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
mBC	Metastatic breast cancer
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
QD	Quaque die, once daily
SAE	Serious adverse event
SOC	Standard of care
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TNBC	Triple-negative breast cancer
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for elacestrant in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Orserdu monotherapy is indicated for the treatment of postmenopausal women, and men, with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer with an ESR1 mutation who have progressed following at least 1 line of endocrine therapy.

2.2.2 Approved indication

Orserdu is used as monotherapy for the treatment of postmenopausal women with estrogen receptor (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation, whose disease has progressed after at least 1 line of endocrine therapy combined with a CDK 4/6 inhibitor.

2.2.3 Requested dosage

Summary of the requested standard dosage:
- Select patients for treatment with Orserdu based on the presence of ESR1 mutations.
- The recommended dosage of Orserdu is 1× 345 mg tablet taken orally, once daily, with food
- Dose interruption, reduction, or permanent discontinuation may be required due to adverse reactions.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	5 May 2023
Formal control completed	15 May 2023
List of Questions (LoQ)	12 September 2023
Response to LoQ	12 November 2023
Preliminary decision	31 January 2024
Response to preliminary decision	12 March 2024
Final decision	4 June 2024
Decision	approval

3 Medical context

Breast cancer (BC) is the most frequently diagnosed cancer in women in the vast majority of countries and is the leading cause of cancer death in women in over 100 countries. Male BC is rare, representing approximately 1% of cancers that occur in men and approximately 1% of all BCs worldwide (Gucalp A et al. Male breast cancer: a disease distinct from female breast cancer. Breast Cancer Res Treat. 2019 Jan;173(1):37-48).

BC is categorised into 3 major subtypes based on the presence or absence of molecular markers for hormone receptors (HR), i.e. estrogen receptors (ER) and progesterone receptors (PR), and human epidermal growth factor 2 (HER2, also known as ERBB2): HR-positive/ HER2-negative BC, HER2-positive BC, and triple-negative BC (TNBC) lacking all 3 standard molecular markers.

Male BC is almost exclusively HR-positive and is associated with an increased prevalence of *BRCA2* germline mutations, especially in men with increased risk for developing high-risk BC, while TNBC is very rare in men.

International guidelines (ESMO and NCCN) recommend either an aromatase inhibitor or fulvestrant, combined with a CDK4/6 inhibitor or targeted agents for eventual specific mutations for first-line treatment of patients with estrogen receptor (ER)-positive, HER2-negative, advanced or metastatic breast cancer in the absence of a visceral crisis endocrine treatment (ET). For second-line treatment the combination of CDK4/6 inhibitors + fulvestrant is available for patients who have not received CDK4/6 inhibitors previously.

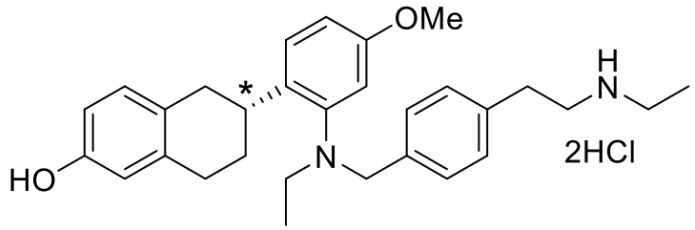
Other options in the second-line setting are the use of sequential ET (fulvestrant or aromatase inhibitors, depending on the ET used in the first line) or everolimus in combination with ET. Patients with PIK3CA or BRCA mutations can be treated with PI3K inhibitors or PARP inhibitors, respectively.

A substantial proportion of patients with ER-positive breast cancer develops endocrine resistance, with genomic and epigenetic alterations of the estrogen receptor 1 (ESR1) gene that encodes for the ER being one of the causes. Mutations of the ESR1 gene have a high prevalence (20-40%) in patients with metastatic breast cancer (mBC) who have previously received ET. Many breast cancers resistant to aromatase inhibitors or tamoxifen still depend on ER signalling and show a partial sensitivity to treatment with the only currently available selective estrogen receptor degrader fulvestrant, which is only available for intramuscular injection. However, patients with ESR1 mutant cancers have been shown to have reduced PFS rates with fulvestrant as compared to patients with wild-type tumours, and more effective treatment options are needed for these patients.

4 Quality aspects

4.1 Drug substance

INN: Elacestrant dihydrochloride
Chemical name: (R)-6-(2-(N-ethyl(4-(2-(ethylamino)ethyl)benzyl)amino)-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol dihydrochloride
Molecular formula: $C_{30}H_{40}Cl_2N_2O_2$
Molecular mass: 531.56 g/mol
Molecular structure:



Chiral center denoted by asterisk (*)

Physicochemical properties: White to off-white to grey solid, soluble in diluted HCl, practically insoluble in aqueous solutions above pH 5.9 and organic solvents. Not hygroscopic. Polymorphism has been observed for elacestrant dihydrochloride.

Synthesis: Elacestrant dihydrochloride is synthesised in 7 main steps using well-defined starting materials with acceptable specifications.

Specification: In order to ensure a consistent quality of elacestrant, the specifications include all relevant test parameters as recommended by the relevant ICH Guidelines.

Stability: Appropriate stability data have been presented for 3 production batches. Based on these results, a satisfactory re-test period has been established when stored in low density polyethylene (LDPE) bags (primary packaging) and aluminium bags (secondary packaging).

4.2 Drug product

Description and composition: The drug product is an immediate-release film-coated tablet, manufactured in 2 strengths (86 mg and 345 mg). The 86 mg tablets are biconvex, blue to light blue coloured, round-shaped with “ME” debossed on one side and plain on the other. The 345 mg tablets are biconvex, blue to light blue coloured, oval-shaped with “MH” debossed on one side and plain on the other.

Manufacture: Excipients and elacestrant dihydrochloride drug substance are weighed and mixed. The pre-blend is dry granulated using a roller compactor. The extra-granular excipients are added, mixed, and compressed on a rotary tablet press using round tooling for the 86 mg and oval tooling for the 345 mg-strength tablets. Elacestrant tablets, 86 mg and 345 mg, are coated with a non-functional aqueous film coating and packaged.

Specification: For the control of the finished product, adequate tests and acceptance criteria for release and shelf-life have been established. The specifications include the parameters appearance (visual examination), identity (UV, HPLC), assay (HPLC), uniformity of dosage units, degradation products (HPLC), water content, dissolution, and microbial tests. Analytical methods have been described and validated according to ICH requirements.

Container closure system: Elacestrant film-coated tablets, 86 mg and 345 mg dosages, are packaged and stored in aluminium (Al)-aluminium (Al) blisters. The blisters are placed in a carton box as non-functional secondary packaging.

Stability: The drug product is photostable. Appropriate stability data have been generated for the drug product in the packaging material intended for commercial use and according to the relevant international guidelines.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

Regarding the marketing authorisation application for Orserdu (elacestrant), the Nonclinical Assessment Division at Swissmedic conducted an abridged evaluation, which was based on the FDA assessment report (Multi-Discipline Review, NDA 217639, January 2023) that was provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Orserdu in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. Safety issues that are of concern for human use were identified in the nonclinical studies. The safety margins are acceptable for a product intended for the treatment of advanced cancer. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals and in the RMP.

There are no safety concerns regarding impurities and excipients.

Based on the available data and the preliminary ERA submitted, it is not possible to draw a conclusion on the potential risk of elacestrant to the environment. Several studies are planned or ongoing, and the respective reports and the final ERA have been requested (post-approval requirement).

6 Clinical aspects

6.1 Clinical pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the FDA. The available assessment reports and product information from this authority were used as a basis for the clinical pharmacology evaluation.

For further details concerning clinical pharmacology and dosing recommendations see the information for healthcare professionals in the appendix of this report.

6.2 Dose finding and dose recommendation

The applicant provided the Phase 1 dose escalation study 005 in patients with ER-positive/HER2-negative mBC, which evaluated the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose of elacestrant.
The starting dose of 200 mg once daily (QD) was selected based on non-clinical efficacy results of xenograft studies in mouse models and the clinical safety of elacestrant in healthy postmenopausal women (RAD1901-001 and RAD1901-004). No dose-limiting toxicity was observed in patients treated with 200 mg QD, 400 mg QD, and 600 mg QD. However, gastrointestinal toxicity was increased in the 600 mg QD dose group, limiting the tolerability of this dose, and 400 mg was therefore selected as the recommended Phase 2 dose. This was supported by the lower target engagement with 200 mg QD in the pharmacodynamic study 10. The dose selection was considered acceptable overall.

6.3 Efficacy

The applicant submitted the pivotal study RAD1901-308 (EMERALD) to support the proposed indication.

This is a randomised, active-controlled, open-label, multicentre study in patients with ER+, HER2-, advanced or metastatic breast cancer (mBC) with disease progression after 1-2 prior lines of endocrine therapy (ET), including as a minimum treatment with a CDK4/6-inhibitor in combination with either an aromatase inhibitor or fulvestrant and as a maximum 1 line of cytotoxic chemotherapy for mBC.

Eligible patients (postmenopausal women or adult men (age ≥ 18 years) with an ECOG of 0-1 must have been appropriate candidates for endocrine monotherapy and must have had measurable disease (or evaluable bone lesions). ER positivity was defined by ≥1% staining by immunohistochemistry (IHC) and HER2 negativity was defined by an IHC result of 0 or 1+ or a negative result of in situ hybridisation.

Eligible patients were randomised 1:1 to either elacestrant 400 mg QD or standard of care (SOC) endocrine treatment with fulvestrant (after prior use of an aromatase inhibitor) or an aromatase inhibitor (after prior use of fulvestrant). Stratification factors were ESR1 mutational status (mutated or not mutated), prior fulvestrant use (yes vs no), and visceral metastases (yes vs no). Crossover was not allowed in the study. ESR1 testing was performed centrally using Guardant360, a test for detection of biomarkers utilising circulating tumour DNA (ctDNA).

The primary endpoint was progression-free survival (PFS) assessed by blinded imaging review committee (BIRC) in ESR1-mutated patients and in all patients (with and without ESR1 mutations or with unknown mutation status). Overall survival (OS) in ESR1-mutated and in all patients was a key secondary endpoint.

In total, 478 patients were randomised to either elacestrant (n=239) or SOC (n=239). 237 patients in the elacestrant and 230 in the SOC arm were treated. Of the 230 treated patients in the SOC arm, 162 received fulvestrant and 68 an aromatase inhibitor. Of 239 patients in each arm, 115 patients in the elacestrant and 113 patients in the SOC arm had an ESR1 mutation.
As of the data cut-off (DCO) for the planned final PFS analysis (6 September 2021), the majority of patients had discontinued treatment (91.6% in the elacestrant and 93.7% in the SOC arm), most of these due to disease progression (84.5% in the elacestrant and 84.9% in the SOC arm).

Baseline demographic and disease characteristics were balanced overall between the 2 arms. Overall, 7 male patients were included in the study: 6 (2.5%) in the elacestrant arm and 1 (0.4%) in the SOC arm. None of the male patients had an ESR1 mutation. In the ESR1 subgroup (n=115 elacestrant arm and n=113 SOC arm), the median age was 64.0 years in the elacestrant arm vs 63.0 years in the SOC arm. Most patients had an ECOG status of 0 (58.3% in the elacestrant and 54.9% in the SOC arm) and were White (89.4% vs 87.0%).
Consistent with the inclusion criteria, all patients had received 1 or 2 prior lines of endocrine therapy in the advanced or metastatic setting and a maximum of 1 prior line of chemotherapy for advanced/metastatic disease. Additionally, all patients had received prior CDK4/6 inhibitor therapy, as requested per inclusion criterion.

In patients with an ESR1 mutation, the median PFS by BIRC was 3.8 in the elacestrant vs 1.9 months in the SOC arm (HR 0.55 [95% CI 0.39, 0.77], stratified log-rank test p-value = 0.0005). The PFS rate at 12 months was 26.8% in the elacestrant vs 8.2% in the SOC arm.

In patients with an ESR1 mutation, the median OS was 24.2 months in the elacestrant vs 23.5 months in the SOC arm (HR 0.90 [95% CI 0.63, 1.3], p-value = 0.58) after follow-up of 31.3 months.

6.4 Safety

Safety data were reported for the pivotal study 308 at an updated data cut-off (DCO) of 8 July 2022.
Treatment-emergent adverse events (TEAEs) of any grade were observed in 92% of patients in the elacestrant vs 86% of patients in the SOC arm.
The most common TEAEs (incidence ≥10%) in the elacestrant arm were nausea, vomiting, and diarrhoea. TEAEs observed with a higher incidence (Δ ≥ 5%) in the elacestrant vs the SOC arm were nausea, vomiting, constipation, dyspepsia, and decreased appetite.

Grade 3-4 TEAEs were more common in the elacestrant compared to the SOC arm (27% vs 21%). The most common grade 3-4 TEAEs (incidence ≥2%) in the elacestrant arm were nausea, back pain, and bone pain, followed by increased alanine transaminase (ALT) and increased blood pressure. Grade 3-4 TEAEs observed with a higher incidence (Δ ≥ 1%) in the elacestrant arm were nausea, back pain, bone pain, and increased ALT.

TEAEs with an outcome of death were observed in 1.7% of patients in the elacestrant vs 2.6% patients in the SOC arm. Reasons for death were antiphospholipid syndrome, cardiac arrest, diverticulitis, and septic shock (n=1 each) in the elacestrant arm, and arrhythmia, myocardial infarction, COVID-19, pneumonia, gastric perforation, and ischemic stroke (n=1 each) in the SOC arm. None of the deaths was assessed as study drug-related by the investigator.

The rate of serious adverse events (SAEs) was similar between the elacestrant and the SOC arm (12.2% vs 10.9%). The most common SAE in the elacestrant arm was nausea, which was also the only SAE with a higher incidence (Δ ≥ 1%) in comparison to SOC.
TEAEs leading to treatment discontinuation were similar in the elacestrant compared to the SOC arm (6.3% vs 4.3%). The most common reason for treatment discontinuation in the elacestrant arm was nausea.

A higher prevalence of high cholesterol, high triglycerides, and high creatinine was observed in the elacestrant arm.

Please refer to the information for healthcare professionals (Appendix) for further details regarding the overall safety pool.

6.5 Final clinical benefit-risk assessment

The statistically significant median PFS benefit of elacestrant vs SOC in patients with an ESR1 mutation was clinically moderate (3.8 vs 1.9 months, ESMO Magnitude of Clinical Benefit Scale Grade 3). However, the benefit-risk assessment is positive based on the observed PFS benefit, including a 12-month PFS rate of 26.8% in the elacestrant arm vs 8.2% in the SOC arm in combination with an acceptable safety profile, which is in general comparable to that in the SOC arm, with the main difference being an increase in gastrointestinal toxicity.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Orserdu was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow for the rapid identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

ORSERDU® film-coated tablets

Composition

Active substances

Elacestrant (as elacestrant dihydrochloride)

Auxiliary supplies

Tablet core: Silicified microcrystalline cellulose (contains microcrystalline cellulose and colloidal silicon dioxide), crospovidone [E1202], magnesium stearate [E470b].

Film coating: poly(vinyl alcohol) [E1203], titanium dioxide [E171], macrogol 3350 [E1521], talc [E553b], brilliant blue FCF aluminum lacquer [E133].

Dosage form and amount of active ingredient per unit

ORSERDU 345 mg film-coated tablets
Blue to light blue biconvex oval shaped film-coated tablet with MH debossed on one side and plain face on the opposite side. Approximate size: 19.2 mm (length), 10.8 mm (width).

ORSERDU 86 mg film-coated tablets
Blue to light blue biconvex round shaped film-coated tablet with the ME debossed on one side and plain face on the opposite side. Approximate diameter: 8.8 mm.

Indications/applications

ORSERDU is used as monotherapy for the treatment of postmenopausal women with estrogen receptor (ER)-positive, HER2 -negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed after at least one line of endocrine therapy combined with a CDK 4/6 inhibitor.

Dosage/Administration

Treatment must 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 ESR1 mutation in plasma specimens, using a validated test. No test is required if an ESR1 mutation has been detected previously.

- 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.

Delayed or missed doses

If a dose is missed, it can be taken immediately within 6 hours after the time it is usually taken. After more than 6 hours, the dose should be skipped for that day. On the next day, ORSERDU should be taken at the usual time.

If the patient vomits after taking the ORSERDU dose, the patient should not take an additional dose on that day and should resume the usual dosing schedule the next day at the usual time.

Dose adjustment following undesirable effects or interactions

The recommended ORSERDU dose modifications for patients with adverse reactions are provided in Tables 1 and 2.

Table 1: Dose reduction levels for undesirable effects

ORSERDU dose level	**Dose and regimen**	**Number and dose strength of tablets**
First dose reduction	258 mg once daily	Three 86 mg tablets
Second dose reduction	172 mg once daily*	Two 86 mg tablets

*If a further dose reduction to less than 172 mg once daily is required, treatment should be discontinued.

Table 2: Dose modification guidelines for adverse reactions

Severity	**Dose adjustment**
Grade 1	ORSERDU at the current dose level.
Grade 2	Consider discontinuing ORSERDU administration until recovery to Grade ≤ 1 or baseline. Then resume treatment with ORSERDU at the same dose level.
Grade 3	Discontinue ORSERDU administration until recovery to Grade ≤ 1 or baseline. Then resume treatment with ORSERDU at the next lower dose level. In case of recurrence of Grade 3 toxicity, discontinue ORSERDU administration until recovery to Grade ≤ 1 or baseline. Then resume treatment with ORSERDU with a dosage reduced by one further dose level.
Grade 4	Discontinue ORSERDU administration until recovery to Grade ≤ 1 or baseline. Then resume treatment with ORSERDU with a dose reduced by one dose level. If a Grade 4 or intolerable adverse reaction recurs, permanently discontinue ORSERDU.

Use of ORSERDU with CYP3A4 inhibitors and CYP3A4 inducers

Concomitant use of strong or moderate CYP3A4 inhibitors or inducers should be avoided (see "Interactions".

If a strong or moderate CYP3A4 inhibitor or inducer must be used, elacestrant dose adjustment may be needed (see “Warnings and Precautions’’ and "Interactions").

Special dosage instructions

Elderly patients

No dose adjustment is required on the basis of patient age. Limited data are available in patients ≥ 75 years of age (see “Pharmacokinetics”).

Patients with hepatic disorders

No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A). In patients with moderate hepatic impairment (Child-Pugh B), reduce elacestrant dose to 258 mg. ORSERDU has not been studied in patients with severe hepatic impairment (Child-Pugh C), therefore no dosage recommendation can be made for patients with severe hepatic impairment (see "Warnings and Precautions").

Patients with renal disorders

No dose adjustment in subjects with renal impairment is necessary. ORSERDU has not been studied in patients with severe renal impairment, therefore no dose recommendation can be made for patients with severe renal impairment (see “Pharmacokinetics”).

Children and adolescents

ORSERDU is not approved for use in paediatrics.
The safety and efficacy in patients under 18 years of age have not been established.

Administration Schedule

Patients should take their dose of ORSERDU at approximately the same time each day.

Mode of administration

ORSERDU is for oral use.
The tablets should be swallowed whole. They should not be chewed, crushed or split prior to swallowing. ORSERDU should be administered with food to reduce nausea and vomiting (see “Pharmacokinetics”)

Contraindications

ORSERDU is contraindicated in case of hypersensitivity to the active substance or to any of the excipients.

ORSERDU is contraindicated during pregnancy and lactation (see «Pregnancy/lactation» and «Preclinical data»).

Warnings and Precautions

Menopause status
Before starting therapy, LH, FSH and/or oestradiol levels must be determined in patients whose postmenopausal status appears unclear in order to clearly determine their menopausal status.

Hepatic impairment
Elacestrant 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. Administration of ORSERDU should be undertaken with caution at a dose of 258 mg once daily in patients with moderate hepatic impairment (Child-Pugh B) (see "Dosage/Administration''). In the absence of clinical data, ORSERDU is not recommended in patients with severe hepatic impairment (Child-Pugh C). Patients with hepatic impairment should be monitored for adverse reactions (see "Dosage/Administration'' and "Pharmacokinetics").

Thromboembolic events
Thromboembolic events are commonly observed in patients with advanced breast cancer and have been observed in clinical studies with ORSERDU (see Adverse Events). This should be taken into consideration when prescribing ORSERDU to patients at risk.

Dyslipidemia
Hypercholesterolemia and hypertriglyceridemia occurred in patients taking ORSERDU at an incidence of 30% and 30%, respectively. The incidence of Grade 3 and 4 hypercholesterolemia and hypertriglyceridemia were 1% and 4%, respectively (see Undesirable effects).
Monitor lipid profile prior to starting and periodically while taking ORSERDU.

Concomitant use with CYP3A4 inhibitors or inducers
Concomitant use with moderate or strong inhibitors or inducers of CYP3A4 may result in clinically relevant interactions. Concomitant use should be avoided (see "Interactions" and "Dosage/Administration").

Interactions

Pharmacokinetic interactions

Elacestrant is primarily metabolized by CYP3A4 and is a substrate of OATP2B1 (*Organic Anion Transporting Polypeptide 2B1*). Elacestrant inhibits the efflux transporters P-glycoprotein (P-gp) and BCRP (*Breast Cancer Resistance Protein*).

Effect of other medicines on ORSERDU

Moderate and strong CYP3A4 inhibitors

Elacestrant is a substrate of CYP3A4. Concomitant use with a moderate or strong inhibitor of CYP3A4 leads to an increase in exposure to elacestrant, which may result in a higher risk of adverse effects.

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. If a strong

CYP3A4 inhibitor must be used, the elacestrant dose should be reduced to 86 mg once daily, with careful monitoring of tolerability.

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. If a moderate CYP3A4 inhibitor must be used, the dose of Elacestrant should be reduced to 172 mg once daily, with careful monitoring of tolerability. Depending on tolerability, a subsequent dose reduction to 86 mg once daily may be considered for moderate CYP3A4 inhibitors.

If the CYP3A4 inhibitor is discontinued, the elacestrant dose (after 5 half-lives of the CYP3A4 inhibitor) should be increased to the dose used before starting treatment with the CYP3A4 inhibitor

No dose adjustments are required when Elacestrant is used concomitantly with weak CYP3A4 inhibitors.

Moderate and strong CYP3A4 inducers

Elacestrant is a substrate of CYP3A4. Concomitant use with a moderate or strong inducer of CYP3A4 leads to a decrease in the exposure of elacestrant, which may lead to reduced efficacy.

Concomitant administration of elacestrant with moderate or strong CYP3A4 inducers such as phenytoin, rifampicin, carbamazepine, St. John's wort (Hypericum perforatum), bosentan, cenobamate, dabrafenib, efavirenz, etravirine, lorlatinib, pexidartinib, phenobarbital, primidone and sotorasib should be avoided.

If a strong or moderate CYP3A4 inducer must be used for a short duration of time (i.e. ≤ 3 days) or intermittently (i.e. treatment periods ≤ 3 days separated by at least 2 weeks or 1 week + 5 half-lives of the CYP3A4 inducer, whichever is longer), continue elacestrant without increasing the dose.

OATP2B1 inhibitors

Elacestrant is a substrate of OATP2B1 in vitro. Limited data on OATP2B1 inhibitors are available in vivo. Therefore, it cannot be excluded that the concomitant administration of elacestrant and OATP2B1 inhibitors may lead to increased elacestrant exposure and thus to a higher risk of adverse effects. Caution is advised with simultaneous use of Elacestrant and OATP2B1 inhibitors.

Table describes the effect of other drugs on the pharmacokinetics of elacestrant based on the ratio of the geometric mean ratio (GMR) of pharmacokinetic variables taken with/without concomitant medication with 90% confidence intervals (CI).

Table 3: Effect of Other Drugs on Elacestrant

Concomitant Drug	Elacestrant Dose	Geometric Mean Ratio 90% Confidence Interval		Recommendation for concomitant use
		C_{max}	AUC	
CYP3A4 Inhibitors				
Strong Inhibitor Itraconazole (200 mg once daily for 7 days)	172 mg once daily	4.37 [3.96, 4.83]	5.26 [4.69, 5.91]	Avoid concomitant use or if unavoidable reduce the dose of elacestrant to 86 mg
Moderate Inhibitor Fluconazole[a] (200 mg once daily for 15 days)	345 mg single dose	1.59 [1.55, 1.63]	2.34 [2.28, 2.40]	Avoid concomitant use or if unavoidable reduce the dose of elacestrant to 172 mg. Consider subsequent dose reduction to 86 mg based on tolerability.
Mild Inhibitor Cimetidine[a] (400 mg twice daily for 15 days)	345 mg single dose	1.13 [1.12, 1.14]	1.11 [1.11, 1.12]	No dose adjustment
CYP3A4 Inducers				
Strong Inducer Rifampin (600 mg once daily for 7 days)	345 mg single dose	0.2704 [0.2309, 0.3167]	0.1417 [0.1234, 0.1627]	Avoid concomitant use
Moderate Inducer Efavirenz[a] (600 mg once daily for 15 days)	345 mg single dose	0.368 [0.347, 0.390] - 0.561 [0.538, 0.585]	0.268 [0.249, 0.287] - 0.452 [0.429, 0.476]	Avoid concomitant use

[a]Predicted changes in C_{max} and AUC of elacestrant.

Effect of ORSERDU on other medicines

P-gp substrates

Concomitant use of ORSERDU with P-gp substrates may increase their concentrations; this can lead to an increased or increased occurrence of the undesirable effects associated with

the P-gp substrates. The dose of the coadministered P-gp substrates should be reduced according to the information in the respective prescribing information.

BCRP substrates
Concomitant use of ORSERDU with BCRP substrates may increase their concentrations; this can lead to an increase or intensification of the undesirable effects associated with the BCRP substrates. Reduce the dose of co-administered BCRP substrates per their Prescribing Information.

Table describes the effect of elacestrant on the pharmacokinetics of other drugs based on ***Table*** the ratio of the geometric mean ratio (GMR) of pharmacokinetic variables taken with/without concomitant medication with 90% confidence intervals (CI).

Table 4: Effect of Elacestrant on Other Drugs

Concomitant Drug	**Elacestrant Dose**	**Geometric Mean Ratio 90% Confidence Interval**		**Recommendation for concomitant use**
		C_{max}	**AUC**	
Substrate of P-gp				
Digoxin 0.5 mg single dose	345 mg single dose	1.27 [1.07, 1.50]	1.13 [1.00, 1.27]	The use of P-gp substrates should be monitored and the dose of the coadministered P-gp substrates should be reduced according to the information in the respective prescribing information.
Substrate of BCRP				
Rosuvastatin 20 mg, single dose	345 mg single dose	1.45 [1.31, 1.61]	1.23 [1.13, 1.33]	The use of BCRP substrates should be monitored and the dose of the coadministered BCRP substrates should be reduced according to the information in the respective prescribing information.
Proton-pump Inhibitor				
Omeprazole 40 mg daily for 12 days	345 mg single dose	0.938 [0.849 - 1.04]	0.938 [0.886, 0.993]	No dose adjustment
Drug with high plasma protein binding				

Warfarin 25 mg, single dose	345 mg single dose	1.03 [0.928, 1.13]	1.06 [0.981, 1.14]	No dose adjustment

In Vitro Studies

Cytochrome P450 (CYP) Enzymes:

Elacestrant is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A.
Elacestrant is not an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4.

Transporter Systems:

Elacestrant is a substrate for OATP2B1. Based on in vitro data, elacestrant is a P-gp substrate. However, P-gp mediated transport is unlikely to affect the pharmacokinetics of elacestrant at therapeutic doses.
Elacestrant is not an inhibitor of OAT1, OAT3, OCT2, MATE1, MATE2-K, OCT1, OATP1B1, OATP1B3 or OATP2B1.

Pregnancy, lactation

Contraception

Based on the mechanism of action of elacestrant and findings from animal studies on reproductive toxicity, elacestrant can cause foetal harm when administered to pregnant women. Women of childbearing potential, women in climacteric and women who have recently become menopausal should be advised of the need to use reliable contraception during treatment with ORSERDU and beyond one week after the last dose. The pregnancy status of females of reproductive potential should be verified prior to starting treatment with Orserdu. If pregnancy occurs while taking ORSERDU, the patient must be informed of the potential hazard to the foetus and potential risk of miscarriage.

Pregnancy

ORSERDU is contraindicated during pregnancy and lactation (see «Contraindications»).
There is no experience with the use of ORSERDU in pregnant women. Animal studies have shown reproductive toxicity (see "Preclinical data"). ORSERDU should not be used during pregnancy or in women of childbearing potential who are not using contraception. If pregnancy occurs during treatment with ORSERDU, the patient must be informed of the possible danger to the fetus and the possible risk of miscarriage.

Lactation

It is not known whether elacestrant is excreted in human milk. Because of the potential for serious adverse reactions in the breast-fed infant, it is recommended that lactating women should not breast feed during treatment with ORSERDU and for one week after last dose of ORSERDU.

Fertility

There are no data on the possible effects of ORSERDU on human fertility. Based on findings from animal studies (see “Preclinical Data”) and its mechanism of action, elacestrant may impair fertility in females and males of reproductive potential.

Effect on the ability to drive and on the operation of machines

ORSERDU has an influence on the ability to drive or operate machines. However, as fatigue, asthenia and insomnia have been reported in patients treated with ORSERDU (see "Undesirable effects"), patients affected by these adverse effects must exercise caution when driving and operating machinery.

Undesirable effects

Summary of the safety profile

The safety evaluation of Elacestrant is based on 301 patients with breast cancer in three open label studies (RAD1901-105, RAD1901-106, and RAD1901-308) in which patients received elacestrant 400 mg once daily as a single agent. The median treatment duration in the ORSERDU safety population was 85 days (range: 5 to 1288 days).

The most common (≥ 10%) adverse reactions with ORSERDU were nausea, triglycerides increased, cholesterol increased, vomiting, fatigue, dyspepsia, diarrhoea, calcium decreased, back pain, creatinine increased, arthralgia, sodium decreased, constipation, headache, hot flush, abdominal pain, anaemia, potassium decreased, and alanine aminotransferase increased.

The most common Grade ≥3 (≥2%) adverse reactions of elacestrant were nausea (2.7%), AST increased (2.7%), ALT increased (2.3%), anaemia (2%), back pain (2%), and bone pain (2%).

Serious adverse reactions reported in ≥ 1% of patients included nausea, dyspnoea, and thromboembolism (venous).

Adverse reactions leading to discontinuation in ≥ 1% of patients included nausea and decreased appetite.

Adverse reactions leading to dose reduction in ≥ 1% of patients included nausea.

The adverse effects leading to interruptions in ≥ 1% of patients were nausea, abdominal pain, alanine aminotransferase increased, vomiting, rash, bone pain, decreased appetite, aspartate aminotransferase increased, and diarrhoea.

List of undesirable effects

Undesirable effects are classified by MedDRA system organ class and frequency according to the following convention:
"very common" (≥1/10)
"common" (≥1/100, <1/10)

"uncommon" (≥1/1,000, <1/100)
"rare" (≥1/10,000, <1/1,000)
"very rare" (<1/10,000)
"not known" (frequency cannot be estimated from the available data)

Table 5. Adverse reactions in patients treated with elacestrant monotherapy 345 mg in metastatic breast cancer

	Elacestrant N=301	
Infections and infestations	Common	Urinary tract infection
Blood and lymphatic system disorders	Very common	Anaemia (11%)
	Common	Lymphocyte count decreased
Metabolism and nutrition disorders	Very common	Triglycerides increased (30%), Cholesterol increased (30%), Calcium decreased (15%), Decreased appetite (15%), Sodium decreased (14%),
	Common	Potassium decreased
Psychiatric disorders	Common	Insomnia
Nervous system disorder	Very common	Headache (13%)
	Common	Dizziness, Syncope
Vascular disorders	Very common	Hot flush* (13%)
	Uncommon	Thromboembolism (venous)*
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea, Cough*
Gastrointestinal disorders	Very common	Nausea (39%), Vomiting (22%), Diarrhoea (16%), Constipation (13%), Abdominal pain*(13%), Dyspepsia*(21%)
	Common	Stomatitis
Hepatobiliary disorders	Very common	Alanine aminotransferase increased (18%), Aspartate aminotransferase increased (14%)
	Common	Blood alkaline phosphatase increased
	Uncommon	Acute hepatic failure
Skin and subcutaneous disorders	Common	Rash*
	Very common	Arthralgia (15%), Back pain (15%)

Musculoskeletal and connective tissues disorders	Common	Pain in extremity, Musculoskeletal chest pain *, Bone pain
General disorders and administration site conditions	Very common	Fatigue (22%)
	Common	Asthenia
Investigations	Very common	Creatinine increased (15%)

*Incidence represents a grouping of similar terms.
Adverse drug reactions are listed by system organ class and by decreasing frequency.

Description of specific undesirable effects and additional information

Nausea
Nausea was reported in 35% of patients. Grade 3-4 nausea are present in 2.5% of patients. Nausea was generally reported early, with a median time to first onset in 14 days (range: 1 to 490 days). Nausea occurred more frequently in the first cycle, and from cycle 2 onward, the incidence of nausea was generally lower in subsequent cycles (i.e., over time). Prophylactic treatment for nausea was prescribed for 12 (5%) subjects in the elacestrant arm and 28 (11.8%) received an antiemetic for the treatment of nausea during the on treatment period.

Special populations

Elderly population
In Study RAD1901-308, 104 patients treated with elacestrant were ≥ 65 years of age and 40 patients ≥ 75 years of age. Gastrointestinal disorders were reported more frequently in patients aged ≥ 75 years. Monitoring of treatment emergent adverse reactions by the treating physician, should include consideration of the patient's age and comorbidities, when selecting personalised interventions.

The reporting of suspected side effects after approval is of great importance. It enables continuous monitoring of the risk-benefit ratio of the drug. Healthcare professionals are encouraged to report any suspicion of a new or serious side effect via the ElViS (Electronic Vigilance System) online portal. For more information, see www.swissmedic.ch.

Overdosing

The highest dose of elacestrant administered in clinical trials was 1,000 mg per day. Adverse drug reactions reported in association with higher than recommended doses were consistent with the established safety profile (see "Undesirable effects"). The frequency and severity of gastrointestinal disorders (abdominal pain, nausea, dyspepsia, and vomiting) appeared to be dose-dependent. There is no known antidote in case of ORSERDU overdose. Patients should be closely monitored and supportive treatment of overdose should be provided (see "Dosage/Administration" and "Warnings and Precautions").

Properties/Effects

ATC code

L02BA04

Action

Elacestrant, a tetrahydronaphthalene compound, is a potent, selective, orally active estrogen receptor α (ERα) antagonist and degrader.

Pharmacodynamics

Elacestrant inhibits estradiol-dependent and estradiol-independent growth of ERα-positive breast cancer cells, including models with estrogen receptor 1 gene mutations and models with resistance to fulvestrant or cyclin-dependent kinase 4/6 inhibitors. Elacestrant exhibited potent antitumor activity in xenograft models derived from patients exposed to multiple endocrine therapies (including fulvestrant-unresponsive xenograft models and models with estrogen receptor 1 gene mutations).

In patients with ER+ advanced breast cancer who had previously received a median of 2.5 lines of endocrine therapy and were treated with 400 mg elacestrant dihydrochloride (345 mg elacestrant) daily, the median reduction in tumor 16α-18F-fluoro-17β-estradiol (FES) uptake from baseline to day 14 was 88.7%. This demonstrates reduced ER availability and antitumor activity as measured by FES PET/CT images in patients who had previously received endocrine therapies.

Cardiac electrophysiology

ORSERDU does not cause a mean increase in QTc interval > 20 msec at the approved recommended dose.

Clinical efficacy

The efficacy and safety of ORSERDU in patients with ER+/HER2- advanced breast cancer following prior endocrine therapy in combination with a CDK4/6 inhibitor were evaluated in Study RAD1901-308. This was a randomized, open-label, active-controlled, multicenter clinical trial in which ORSERDU was compared with standard therapy (fulvestrant in patients who were pre-treated with aromatase inhibitors in the metastatic situation, or aromatase inhibitors in patients who had already received fulvestrant in the metastatic situation). Both postmenopausal women and men with tumor recurrence or progression after at least 1 and no more than 2 previous endocrine therapies were eligible to participate in the study. Patients with prior bilateral surgical oophorectomy were considered postmenopausal. All patients had to have an ECOG performance status of 0 or 1 as well as evaluable lesions according to RECIST version 1.1, i.e. measurable disease or sole bone involvement with evaluable lesions. Prior endocrine therapy had to include a combination with CDK4/6 inhibitor therapy and no more than 1 previous line of cytotoxic chemotherapy for metastatic breast cancer. Patients had to be suitable candidates for endocrine monotherapy. Patients with symptomatic visceral metastasis, with untreated or progressive CNS metastases, with cardiac comorbidity, and those with severe hepatic impairment were excluded from participation.

A total of 478 patients were randomized in a 1:1 ratio to receive either 400 mg of elacestrant dihydrochloride (345 mg elacestrant) or standard of *care* (SOC) daily (239 randomized to ORSERDU and 239 to SOC), including a total of 228 patients (47.7%) with ESR1 mutations at baseline (115 patients on ORSERDU and 113 patients on SOC). Randomization was stratified according to ESR1 mutation status (ESR1-mut vs. ESR1-mut-nd [no *ESR1*

mutations detected]), prior treatment with fulvestrant (yes vs. no), and visceral metastasis (yes vs. no). ESR1 mutation status was determined by measuring *circulating tumor deoxyribonucleic acid* (ctDNA) in the blood and was limited to ESR1 missense mutations in the ligand-binding domain (between codes 310 and 547). Of the 113 patients with ESR1 mutation randomized to the SOC arm, 83 had received fulvestrant and 30 an aromatase inhibitor (AI), namely anastrozole, letrozole or exemestane. Prior treatment with fulvestrant was reported in 23.5% of patients with ESR1 mutations randomized to Orserdu and 24.8% of patients randomized to SOC.

The median age of patients (ORSERDU vs. standard therapy) at baseline was 64.0 years (range: 28-89) vs. 63.0 (range: 32-83), with 45.6% over 65 years of age (46.1 vs. 45.1). All of the study participants with ESR1 mutations were women and most were white (89.4% vs. 87.0%), followed by patients of Asian (5.3% vs. 8.7%), Black or African American (4.3% vs 4.3%) and other/unknown origins (1.1% vs. 0%). Baseline ECOG performance status was 0 (58.3% vs. 54.9%) or 1 (41.7% vs. 45.1%). The demographic characteristics of the study participants with ESR1-mutated tumors were generally representative of the overall population of the study. The median duration of exposure to elacestrant was 2.9 months (range: 0.4 to 24.8).

The primary efficacy endpoint was progression-free survival (PFS), as determined by an Independent Review Committee (IRC) in all patients, i.e., including patients with an *ESR1* mutation, and in patients with *ESR1 mutations.* Overall survival was an important secondary efficacy endpoint. The efficacy results for patients with ESR1 mutations are presented in Table 6.

Table 6: Efficacy results in patients with ESR1 mutations (evaluated by a blinded imaging review committee)

	ORSERDU	**Standard therapy**
Progression-free survival (PFS)	**N = 115**	**N = 113**
Number of PFS events, n (%)	62 (53.9)	78 (69.0)
Median PFS in months* (95% CI)	3.78 (2.17, 7.26)	1.87 (1.87, 2.14)
Hazard ratio (95% CI)	0.546 (0.387, 0.768)	
p-value (stratified log-rank test)	0.0005	
6-month PFS Rate (%)(95% CI)	40.76 (30.10-51.43)	19.14 (10.52-27.76)
12-month PFS Rate (%)(95% CI)	26.76 (16.17-37.36)	8.19 (1.26-15.12)
Overall Survival *(*OS)	**N = 115**	**N = 113**
Number of OS events, n (%)	61 (53)	60 (53.1)
Median OS in months* (95% CI)	24.18 (20.53, 28.71)	23.49 (15.64, 29.90)
Hazard ratio (95% CI)	0.903 (0.629, 1.298)	
p-value (stratified long-rank test)	Not statistically significant	
6 month OS Rate (%)	92.79 (87.97 - 97.60)	84.36 (77.32 - 91.40)
12 month OS Rate (%)	83.11 (75.98 - 90.25)	74.38 (65.88 - 82.89)
18 month OS Rate (%)	69.09 (60.15 - 78.04)	53.27 (43.50 - 63.04)
24 month OS Rate (%)	50.71 (40.91 - 60.52)	49.02 (39.18 - 58.87)

CI = confidence interval; ESR1 = estrogen receptor 1; PFS = *progression-free survival*.
Data cut-off dates are 06 September 2021 for PFS and 02 September 2022 for OS.

Pediatrics

Swissmedic has granted ORSERDU an exemption from the obligation to submit results of studies in all paediatric age groups in the field of breast cancer (see "Dosage/Administration").

Pharmacokinetics

ORSERDU C_{max} and AUC increase slightly more than proportional to dose for doses ≥50 mg (salt form). The C_{max} and AUC of elacestrant increase more than proportionally over a dosage range from 43 mg to 862 mg once daily (0.125 to 2.5 times the approved recommended dosage).

Absorption

Following oral administration, elacestrant was rapidly absorbed and reached C_{max} within 1-4 hours. The oral bioavailability of ORSERDU is approximately 10%. Steady state is achieved with once-daily administration on day 6 after the start of treatment. The mean accumulation ratio based on AUC_{0-24h} is 2-fold after 7 days of daily oral administration. The steady-state mean (%CV) maximum concentration (C_{max} of elacestrant is 119 ng/mL (43.6%) and AUC_{0-24h} is 2440 ng*h/mL (44.3%) after administration of the recommended dose of 345 mg once daily.

Effect of food

Administration of elacestrant 345 mg tablet with a high-fat meal increased C_{max} by 42% and increased $AUC_{0-\infty}$ by 22%, respectively, compared to fasted administration.

Distribution

Plasma protein binding of elacestrant is > 99% and is independent of concentration.
Based on a population pharmacokinetic analysis, the apparent peripheral volume of distribution of elacestrant at steady state was 5411 L and the central volume of distribution was 422 L.

Metabolism

Elacestrant is primarily metabolized by CYP3A4, possibly with a small contribution of CYP2A6 and CYP2C9. After administration of a single radioactive dose of 345 mg, elacestrant was a minor (< 10% of plasma radioactivity) component in human plasma. The 4-[2-(ethylamino) ethyl]benzoic acid (EAEBA) glucuronide was a major metabolite in human plasma (about 41% of plasma radioactivity).

Elimination

The half-life of elacestrant is approximately 30-50 hours. At steady state, the mean (% CV) predicted clearance of elacestrant is 186 l/h (43.5%).

Following a single oral dose of 345 mg of radiolabeled elacestrant, 82% (34% unmodified parent substance) was recovered in feces and 7.5% (<1% unmodified parent substance) in

the urine. Elacestrant renal clearance is very low (≤ 2.3 mL/min) and it was eliminated by oxidative metabolism and fecal excretion.

Kinetics of special patient groups

Based on population pharmacokinetic analyses, no dose adjustment is warranted based on body weight (41 - 143 kg), age (24 - 89 years) and gender is not required.

Hepatic impairment

The C_{max} and AUC values were similar between subjects in the mild hepatic impairment group (Child-Pugh A) and the normal hepatic function group upon single dose administration of elacestrant 176 mg. There were significant increases in AUC_{0-t} (76%) and $AUC_{0-\infty}$ (83%) in the moderate hepatic impairment group (Child-Pugh B) compared to the normal hepatic function group. The C_{max} values were similar between the normal and moderate impairment groups. Elacestrant has not been studied in subjects with severe hepatic impairment (Child-Pugh C).

Renal impairment

The renal excretion of elacestrant is minimal, therefore no pharmacokinetic studies in patients with renal impairment have been conducted. Elacestrant has not been studied in patients with severe renal impairment.

Preclinical data

Repeated-dose toxicity

Elacestrant showed low acute toxicity. In repeated dose toxicity studies in rats and cynomolgus monkeys, the antiestrogenic activity of elacestrant was responsible for the effects seen, particularly in the female reproductive system at doses ≥10 mg/kg in both rats and monkeys (see below) with systemic exposures of 0.8- and 0.3-fold the clinical one, respectively, but also in other organs sensitive to hormones such as mammary gland, pituitary, and testes. In addition, in long-term studies (26 weeks in rats with doses up to 50 mg/kg/day and 39 weeks in cynomolgus monkeys with doses up to 30mg/kg/ day), increased vacuolization of the mucosal epithelium of the non-glandular stomach was observed in rats and vacuolated macrophage infiltrates in the small intestine were recorded in rats at doses ≥25 mg/kg (2.1-fold the human exposure). In the monkeys, this effect occurred at a systemic exposure close to 0.3 times the exposure in humans.

Genotoxicity

Elacestrant showed no genotoxic potential in the Ames test, chromosomal aberrations in human lymphocytes in vitro, and in the in vivo micronucleus assay in rats.

Carcinogenicity

Carcinogenicity studies have not been performed with elacestrant.

Reproductive toxicity

Fertility studies in animals have not been conducted.

In repeated dose toxicity studies lasting up to 26 weeks in rats up to 50 mg/kg and 39 weeks in cynomolgus monkeys up to 30 mg/kg, adverse reactions potentially impairing fertility were observed in the female reproductive organs, including atrophy of the vagina, cervix and uterus, and ovarian follicular cysts at doses ≥ 10 mg/kg/day in rats and cynomolgus monkeys (≥0.8 and 0.3 fold the human AUC at the recommended dose, respectively). Decreased cellularity of Leydig cells degeneration/atrophy of the testicular epithelium were observed in male rats at a dose of 50 mg/kg/day (approximately 2.6 fold the human AUC at the recommended dose)

In an embryo-fetal development study in pregnant rats, administration of oral doses of elacestrant up to 30 mg/kg/day during the period of organogenesis resulted in maternal toxicity (reduced body weight gain, low food intake, red vulvar discharge) and embryo-fetal mortality (increased resorptions, post-implantation loss, and decreased number of live fetuses) at ≥ 3 mg/kg/day (approximately 0.1 times the human AUC at the recommended dose). Other adverse effects included decreased fetal weight and external malformations of the limbs (hyperflexion, malrotation) and head (arched, malformed, flattened) with corresponding skeletal malformations of the skull at doses ≥ 10 mg/kg/day (approximately 0.5 times the human AUC at the recommended dose).

Toxicity studies with juvenile animals

In animal studies in juvenile mice and rats, estradiol increased the weight of the uterus and the thickness of the endometrium, while elacestrant led to a decrease at doses up to and including 100 mg/kg/day, suggesting a minimal risk of elacestrant-induced hyperplasia.

Other Notes

Incompatibilities

Not applicable.

Shelf-lifeDurability

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special storage instructions

Store in the original packaging and not above 30°C.
Keep out of reach of children.

Instructions for handling

Any unused medicinal product or waste material shall be disposed of in accordance with local requirements.

Authorisation number

69417 (Swissmedic)

Packs

Each outer carton contains four blister strips. Each blister strip contains 7 film-coated tablets.

ORSERDU, 345 mg film-coated tablets, 28 tablets (B)

ORSERDU, 86 mg film-coated tablets, 28 tablets (B)

Marketing authorisation holder

Stemline Therapeutics Switzerland GmbH, Zug

Status of information

January 2024