ELACESTRANT

Indication
Elacestrant monotherapy is indicated for the treatment of postmenopausal women, and men, with oestrogen receptor (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.

Regimen details
345mg once daily (till progression or unacceptable toxicity)

Cycle frequency
Continuous (dispense monthly or as appropriate)

Number of cycles
Till progression or unacceptable toxicity

Administration
Oral tablet, Maximum dose is 345mg daily, tablet sizes 345mg and 86mg
Taken at a regular time each day with food
Delayed doses can be taken within 6hrs of the normal time, missed doses should be skipped till the next day
Vomiting after taking elacestrant – omit dose till the following day

Pre-medication
Nil required

Emetogenicity
Mild

Additional supportive medication
Loperamide and metoclopramide with 1st cycle

Extravasation
Not applicable

Investigations – pre first cycle
Confirmed ESR-1 mutation
Standard pre-SACT tests

Investigations –pre subsequent cycles
FBC, U+E (including creatinine), LFT (including AST)

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 30 mL/min (see below)
Bilirubin	≤ 1.5 x ULN (see below)
AST	< 1.5 x ULN (see below)

Dose modifications

Reduce to 258mg once daily (3 x 86mg tablets) if dose reduction required.
If not tolerated stop, there are no further dose reductions

Grade 2:

Consider interruption of Elacestrant until recovery to Grade ≤ 1 or baseline. Then resume at the same dose level

Grade 3:

Interrupt Elacestrant until recovery to Grade ≤ 1 or baseline. The dose should be reduced to 258 mg when resuming therapy. If the Grade 3 toxicity recurs, interrupt until recovery to Grade ≤ 1 or baseline. The reduced dose of 258 mg may be resumed if at the discretion of the treating physician if the patient is benefiting from treatment. If a Grade 3 or intolerable adverse reaction recurs, permanently discontinue Elacestrant

Grade 4:

Interrupt Elacestrant until recovery to Grade ≤ 1 or baseline. The dose should be reduced to 258 mg when resuming therapy. If a Grade 4 or intolerable adverse reaction recurs, permanently discontinuation

Adverse effects - for full details consult product literature/ reference texts

Serious side effects

HPB: acute hepatic failure (uncommon)

Frequently occurring side effects

Infections and infestations: urinary tract infections

Blood and lymphatic disorders; anaemia and decreased lymphocyte count

Metabolism and nutrition: reduced appetite

Psychiatric disorders: insomnia

CNS: headache, dizziness and syncope

Vascular; flush and venous thromboembolism

Respiratory: Cough and dyspnoea

GI: nausea, vomiting, diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis

Skin: rash

MSK: pain in extremities, bone pain, musculoskeletal chest pain

Investigations: increase in AST, TG, ALT, cholesterol, Creatinine, reduction in Calcium, Sodium and Potassium

Other side effects

Nausea Nausea was reported in 35% of patients. Grade 3-4 nausea events were reported in 2.5% of patients. Nausea was generally reported early, with a median time to the first onset 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.

Elderly In the RAD1901-308 study, 104 patients who received elacestrant were ≥ 65 years and 40 patients were ≥ 75 years. 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.

Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow card system

Overdose: The highest dose of ORSERDU administered in clinical studies was 1000 mg per day. The adverse drug reactions reported in association with doses higher than the recommended dose were consistent with the established safety profile (see section 4.8). The frequency and severity of gastrointestinal disorders (abdominal pain, nausea, dyspepsia and vomiting) appeared to be dose-related. There is no known antidote for an overdose of ORSERDU. Patients should be closely monitored and treatment of overdose should consist of supportive treatment.

Significant drug interactions – for full details consult product literature/ reference texts

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

Effect of other medicinal products on Elacestrant

CYP3A4 Inhibitors

Co-administration of the strong CYP3A4 inhibitor itraconazole (200 mg once daily for 7 days) with ORSERDU (172 mg once daily for 7 days) increased elacestrant plasma exposure (AUCinf) and the peak concentration (Cmax) in healthy subjects 5.3 and 4.4-fold, respectively.

Physiologically based pharmacokinetic (PBPK) simulations in cancer patients suggested that the concomitant administration of multiple daily doses of elacestrant 345 mg and itraconazole 200 mg may increase elacestrant steady-state AUC and Cmax 5.5- and 3.9-fold, respectively, which may increase the risk of adverse reactions.

PBPK simulations in cancer patients suggested that concomitant administration of multiple daily doses of elacestrant 345 mg with moderate CYP3A4 inhibitors may increase elacestrant steady-state AUC and Cmax by 2.3- and 1.9-folds, respectively, with fluconazole (200 mg once daily), and by 3.9- and 3.0-folds, respectively, with erythromycin (500 mg four times a day), which may increase the risk of adverse reaction. CYP3A4 Inducers

Co-administration of the strong CYP3A4 inducer rifampicin (600 mg once daily for 7 days) with a single dose of elacestrant345 mg decreased elacestrant plasma exposure (AUCinf) and the peak concentration (Cmax) in healthy subjects by 86% and 73%, respectively, which may decrease elacestrant activity.

PBPK simulations in cancer patients suggested that the concomitant administration of multiple daily doses of elacestrant 345 mg and rifampicin 600 mg may decrease elacestrant steady-state AUC and Cmax by 84% and 77%, respectively, which may decrease elacestrant activity.

PBPK simulations in cancer patients suggested that the concomitant administration of multiple daily doses of elacestrant 345 mg and the moderate CYP3A4 inducer efavirenz (600 mg) may decrease elacestrant steady-state AUC and Cmax by 57% and 52%, respectively, which may decrease elacestrant activity.

OATP2B1 inhibitors

Elacestrant is a substrate of OATP2B1 in vitro. As it cannot be excluded that the coadministration of OATP2B1 inhibitors may increase the exposure of elacestrant, which may increase the risk of adverse reactions, caution is recommended in case of concomitant use of ORSERDU with OATP2B1 inhibitors.

Effect of Elacestrant on other medicinal products

P-gp substrates

Co-administration of ORSERDU (345 mg, single dose) with digoxin (0.5 mg, single dose) increased digoxin exposure by 27% for Cmax and 13% for AUC. Digoxin administration should be monitored and its dose reduced as necessary. Concomitant use of elacestrant with other P-gp substrates may increase their concentrations, which may increase the

adverse reactions associated with the P-gp substrates. The dose of coadministered P-gp substrates should be reduced according to their Summary of Product Characteristics.

BCRP substrates

Co-administration of ORSERDU (345 mg, single dose) with rosuvastatin (20 mg, single dose) increased rosuvastatin exposure by 45% for Cmax and 23% for AUC. Rosuvastatin administration should be monitored and its dose reduced as necessary. 7 Concomitant use of ORSERDU with other BCRP substrates may increase their concentrations, which may increase the adverse reactions associated with the BCRP substrates. The dose of coadministered BCRP substrates should be reduced according to their Summary of Product Characteristics.

Additional comments

Women of childbearing potential/Contraception in males and females

Elacestrant should not be used during pregnancy or in women of childbearing potential not using contraception. Based on the mechanism of action of elacestrant and findings from reproductive toxicity studies in animals, Elacestrant can cause foetal harm when administered to pregnant women. Females of reproductive potential should be advised to use effective contraception during treatment with elacestrant and one week after the last dose.

Pregnancy

There are no data from the use of elacestrant in pregnant women. Studies in animals have shown reproductive elacestrant should not be used during pregnancy or in women of childbearing potential not using contraception. The pregnancy status of females of reproductive potential should be verified prior to starting treatment with Elacestrant. If pregnancy occurs while taking ORSERDU, the patient must be informed of the potential hazard to the foetus and potential risk of miscarriage.

Breast-feeding

It is unknown whether elacestrant/metabolites are 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 Elacestrant and one week after the last dose of elacestrant. Fertility Based on findings from animal studies and its mechanism of action, elacestrant may impair fertility in females and males of reproductive potential

References

NICE Guidance https://www.nice.org.uk/guidance/indevelopment/gid-ta11263
SMPC elacestrant https://www.medicines.org.uk/emc/product/15398/smpc

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THIS PROTOCOL HAS BEEN DIRECTED BY DR M HOGG DESIGNATED LEAD CLINICIAN FOR BREAST CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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