NOVARTIS

FEMARA

(letrozole)

2,5 mg film-coated tablets

Professional Information

Document status: Final

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SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

FEMARA 2,5 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2,5 mg letrozole.

Excipient with known effect:

- Contains sugar: each tablet contains 61,5 mg of lactose (monohydrate)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dark yellow, round, slightly biconvex tablets with bevelled edges. One side bears the imprint "FV", the other "CG".

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.
- Extended adjuvant treatment of early invasive breast cancer in post-menopausal women who have received prior standard adjuvant tamoxifen therapy for five years.

- First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer.
- Advanced breast cancer after relapse or disease progression, in women with natural or artificially induced postmenopausal endocrine status, who have previously been treated with anti-oestrogens.
- Neo-adjuvant treatment of postmenopausal women with hormone receptor positive, HER-2 negative breast cancer where chemotherapy is not suitable and immediate surgery is not indicated.

FEMARA is not indicated in hormone receptor negative disease.

4.2 Posology and method of administration

Posology

Adults

The recommended dose of FEMARA is 2,5 mg once daily.

In the adjuvant and extended adjuvant setting, treatment with FEMARA should continue for 5 years or until disease relapse/recurrence occurs, whichever comes first. In patients with metastatic disease, treatment with FEMARA should continue until tumour progression is evident. In the neoadjuvant (preoperative) setting, treatment with FEMARA should be continued for 4 to 8 months in order to establish optimal tumour reduction. If the response is not adequate, treatment with FEMARA should be discontinued, surgery scheduled and/or further treatment options discussed with the patient.

Special Populations

Elderly patients (age 65 years and over):

No dose adjustment is required for elderly patients.

Renal impairment:

No dosage adjustment of FEMARA is required for patients with renal insufficiency with creatinine clearance (CLcr) ≥ 10 mL/min. Insufficient data are available to establish dosage recommendations for patients with a creatinine clearance of ≤ 10 mL/min (see sections 4.4 and 5.2).

Hepatic impairment:

No dose adjustment of FEMARA is required for patients with mild to moderate hepatic impairment (Child Pugh score A and B). Insufficient data are available for patients with severe hepatic impairment (Child Pugh score C) and should be kept under close supervision (see section 4.4).

Paediatric population:

FEMARA is not recommended for the use in children and adolescents. The safety and efficacy in children and adolescents aged up to 17 years have not been established. Limited data are available.

Method of administration

FEMARA should be taken orally and can be taken with or without food.

A missed dose should be taken as soon as the patient remembers. However, if it is almost time for the next dose, the missed dose should be skipped, and the patient should go back to their regular dosage schedule. Doses should not be doubled, because with daily doses over 2,5 mg recommended dose, over-proportionality in systemic exposure was observed (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Premenopausal endocrine status, pregnancy or lactation.
- Severe impairment of hepatic function (Child-Pugh grade C).
- Severe impairment of renal function (creatinine clearance< 10 mL/min).

4.4 Special warnings and precautions for use

Renal impairment

FEMARA has not been investigated in a sufficient number of patients with a creatinine clearance lower than 10 mL/min. The potential risk/benefit to such patients should be carefully considered before administration of FEMARA (see sections 4.3 and 5.2).

Hepatic impairment

In patients with severe hepatic impairment (Child-Pugh C), systemic exposure and terminal half-life were approximately doubled compared to healthy volunteers. Such patients should therefore be kept under close supervision (see sections 4.3 and 5.2).

Bone effects

Osteoporosis and/or bone fractures have been reported with the use of FEMARA. Therefore, monitoring of overall bone health is recommended during treatment.

Tendon disorders

The use of third generation aromatase inhibitors, including letrozole, were found to be associated with tendonitis and tenosynovitis in randomised controlled trials. Tendon rupture was found to be a potential risk. Tendonitis and tenosynovitis were estimated to be of uncommon occurrence, and tendon rupture of rare occurrence. Monitor patients for signs and symptoms of tendon disorders during treatment with FEMARA.

Menopausal status

In patients whose menopausal status is unclear, luteinising hormone (LH), follicle –stimulating hormone (FSH) and/or oestradiol levels should be measured before initiating treatment with FEMARA. Only women of confirmed postmenopausal endocrine status should receive FEMARA.

Fertility

The pharmacological action of FEMARA is to reduce oestrogen production by aromatase inhibition. In premenopausal women, the inhibition of oestrogen synthesis leads to feedback

increases in gonadotropin (LH, FSH) levels. Increased FSH levels in turn stimulate follicular growth and can induce ovulation.

Interactions

Co-administration of FEMARA with tamoxifen, other anti-oestrogens or oestrogen-containing therapies should be avoided as these substances may diminish the pharmacological action of FEMARA (see section 4.5).

Contains lactose

Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take FEMARA.

4.5 Interaction with other medicines and other forms of interaction

FEMARA is mainly metabolised in the liver and the cytochrome P450 enzymes CYP3A4 and CYP2A6 mediate the metabolic clearance of FEMARA. Therefore, the systemic elimination of FEMARA may be influenced by medicines known to affect the CYP3A4 and CYP2A6. The metabolism of FEMARA appears to have low affinity for CYP3A4 because the enzyme could not be saturated at concentrations more than 150-fold higher than those observed in plasma for FEMARA at steady-state in the typical clinical situation.

Medicine that may increase FEMARA serum concentrations

Inhibitors of CYP3A4 and CYP2A6 activities could decrease the metabolism of FEMARA and thereby increase plasma concentrations of FEMARA. The concomitant administration of medications that strongly inhibits these enzymes (strong CYP3A4 inhibitors: including but not limited to ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin and telithromycin; CYP2A6 (e.g. methoxsalen) may increase exposure to FEMARA. Therefore, caution is recommended in patients for whom strong CYP3A4 and CYP2A6 inhibitors are administered.

Medicine that may decrease FEMARA serum concentrations

Inducers of CYP3A4 activity could increase the metabolism of FEMARA and thereby decrease plasma concentrations of FEMARA. The concomitant administration of medications that induce CYP3A4 (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital and St. John's Wort) may reduce exposure to FEMARA. Therefore, caution is recommended in patients for whom strong CYP3A4 inducers are administered.

Co-administration of FEMARA and tamoxifen 20 mg daily resulted in a reduction of FEMARA plasma levels by 38 % on average. Clinical experience in the second-line breast cancer trials indicates that neither the therapeutic effect of FEMARA therapy nor the occurrence of adverse reactions is increased if FEMARA is administered immediately after tamoxifen. The mechanism of this interaction is unknown.

Medicine that may have their systemic serum concentrations altered by FEMARA

In vitro, FEMARA inhibits the cytochrome P450 isoenzymes CYP2A6 and, moderately, CYP2C19, but the clinical relevance is unknown. Caution is therefore indicated when giving FEMARA concomitantly with medicinal products whose elimination is mainly dependent on CYP2C19 and whose therapeutic index is narrow (e.g. phenytoin, clopidogrel). No substrate with narrow therapeutic index is known for CYP2A6.

Clinical interaction studies with cimetidine (a known non-specific inhibitor of CYP2C19 and CYP3A4 and warfarin (sensitive substrate for CYP2C9 with narrow therapeutic window and commonly used as co-medication in the target population of FEMARA) indicated that the coadministration of FEMARA with these medicines does not result in clinically significant medicine interactions.

Additionally, in a large clinical trial there was no evidence of clinically relevant interaction in patients receiving other commonly prescribed medicines (e.g. benzodiazepines; barbiturates; NSAIDs such as diclofenac sodium, ibuprofen; paracetamol; furosemide; omeprazole).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

FEMARA should only be used in women with a clearly established postmenopausal status. The doctor needs to discuss the necessity of adequate contraception with women who have the potential to become pregnant including women who are perimenopausal or who recently became postmenopausal, until their postmenopausal status is fully established.

Pregnancy

FEMARA is contra-indicated during pregnancy.

FEMARA may cause foetal harm when administered to a pregnant woman. The patient should be apprised of the potential risk to the foetus, if FEMARA is used during pregnancy or if the patient becomes pregnant while taking this medicine.

There are no clinical trials conducted in pregnant women with FEMARA. There have been post-marketing reports of spontaneous abortions and congenital anomalies in infants of mothers who have taken FEMARA (see section 4.3).

Cases of birth defects (labial fusion, ambiguous genitalia) have been reported in infants born to woman exposed to off label use (infertility treatment, ovulation induction) of FEMARA during pregnancy.

Lactation

FEMARA is contraindicated during lactation (see section 4.3)

It is not known if FEMARA is excreted in human milk. There are no data on the effects of FEMARA on the breastfed child or the effects of FEMARA on milk production.

4.7 Effects on ability to drive and use machines

Fatigue, dizziness and somnolence have been observed with the use of FEMARA. Patients should be advised that their physical and/or mental abilities required for operating machinery or driving a car may be impaired.

4.8 Undesirable effects

Summary of the safety profile:

FEMARA was generally well tolerated across all studies as first-line and second-line treatment for advanced breast cancer, as adjuvant treatment of early breast cancer and as extended adjuvant treatment in women who have received prior standard tamoxifen therapy. Approximately one third of the patients treated with FEMARA in the metastatic and neoadjuvant settings, approximately 70-75 % of the patients in the adjuvant setting (both FEMARA and tamoxifen arms), and approximately 80 % of the patients in the extended adjuvant setting (both FEMARA and placebo arms) can be expected to experience adverse reactions.

The most frequently reported adverse reactions in the clinical studies were hot flushes, hypercholesterolaemia, arthralgia, fatigue, increased sweating and nausea. Many adverse reactions can be attributed to the normal pharmacological consequences of oestrogen deprivation (e.g. hot flushes, alopecia and vaginal bleeding).

Other important additional adverse reactions that may occur with FEMARA are cardiovascular events (including cerebrovascular and thromboembolic events).

The following adverse events, not reported in the advanced or metastatic clinical trials, were noted in the extended adjuvant setting arthralgia/arthritis, osteoporosis and bone fractures.

The following adverse drug reactions, listed in Table 1, were reported from clinical studies and from post marketing experience with FEMARA.

Tabulated summary of adverse drug reactions from clinical trials and from post marketing experience with FEMARA

Table 1

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common ≥10 %; common ≥1 % to <10 %; uncommon ≥ 0, 1 % to <1 %; rare ≥ 0, 01 % to <0, 1 %; very rare <0, 01 %, including not known/cannot be estimated and isolated reports.

Infections and infestations Uncommon	Urinary tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps) Uncommon	Tumour pain[1]
Immune system disorders Not known	Anaphylactic reaction
Blood and the lymphatic system disorders Uncommon	Leukopenia

Metabolism and nutrition disorders Very common Common	 Hypercholesterolemia Decreased appetite, increased appetite
Psychiatric disorders Common Uncommon	 Depression Anxiety (including nervousness), irritability
Nervous system disorders Common Uncommon	 Headache, dizziness, vertigo Somnolence, insomnia, memory impairment, dysaesthesia (including paraesthesia, hypoaesthesia), dysgeusia, cerebrovascular accident, carpal tunnel syndrome
Eye disorders	Cataract, eye irritation, blurred vision

Uncommon	
Cardiac disorders Common Uncommon	 Palpitations Tachycardia, ischaemic cardiac events (including new or worsening angina requiring surgery, myocardial infarction and myocardial ischaemia)
Vascular disorders Very common Common Uncommon Rare	 Hot flushes Hypertension Thrombophlebitis (including superficial and deep vein thrombophlebitis) Pulmonary embolism, arterial thrombosis, cerebral infarction

Respiratory, thoracic and mediastinal disorders Uncommon	Dyspnoea, cough
Gastrointestinal disorders Common	Nausea, vomiting, dyspepsia, constipation, diarrhoea, abdominal pain
Uncommon	Stomatitis, dry mouth
Hepato-biliary disorders Uncommon	Increased hepatic enzymes, hyperbilirubinaemia, jaundice
Very rare	Hepatitis
Skin and subcutaneous tissue disorders Very common	Hyperhidrosis

Common	Alopecia, dry skin, rash (including erythematous, maculopapular, psoriaform and vesicular rash)
Uncommon	Pruritus, urticaria
Not known	Angioedema, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal, connective tissue and bone disorders	
Very common	Arthralgia
Common	Myalgia, bone pain, osteoporosis, bone fractures, back pain, arthritis
Not known	Trigger finger, tendonitis, tenosynovitis, tendon rupture (see section 4.4)

Renal and urinary disorders Uncommon	Pollakiuria
Reproductive system and breast disorders Common Uncommon	Vaginal haemorrhage Vaginal discharge, vulvovaginal dryness, breast pain
General disorders and administration site conditions Very common Common Uncommon	Fatigue (including asthenia, malaise) Peripheral oedema, chest pain Generalised oedema, pyrexia, mucosal dryness, thirst
Investigations Common	Weight increased

Uncommon	Weight decrease
Injury, poisoning and procedural complications Common[2]	Fall[3]

[1] Adverse drug reactions reported only in the metastatic setting

[2] Frequency determined based on FACE study data

[3] In some cases fall was reported as a consequence of other adverse events such as dizziness and vertigo

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

No specific treatment for overdosage is known; treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

A 21.12 Hormone Inhibitors.

The elimination of oestrogen-mediated stimulatory effects is a prerequisite for tumour response in cases where the growth of tumour tissue depends on the presence of oestrogens. In postmenopausal women, oestrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens- primarily androstenedione and testosterone- to estrone (E1) and oestradiol (E2). The suppression of oestrogen biosynthesis in peripheral tissues and the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme.

Letrozole is a non-steroidal aromatase inhibitor. It inhibits the aromatase enzyme by competitively binding to the haem of the cytochrome P450 subunit of the enzyme, resulting in a reduction of oestrogen biosynthesis in all tissues.

In healthy postmenopausal women, single doses of 0,1 mg, 0,5 mg and 2,5 mg letrozole suppress serum oestrone and oestradiol by 75 to 78 % and 78 % from baseline respectively. Maximum suppression is achieved in 48 to 78 hours.

In postmenopausal patients with advanced breast cancer, daily doses of 0,1 to 5 mg suppress plasma concentration of oestradiol, oestrone, and oestrone sulphate by 75 to 95 % from baseline in all patients treated. With doses of 0,5 mg and higher, many values of oestrone and oestrone sulphate are below the limit of detection in the assays, indicating that higher oestrogen suppression is achieved with these doses. Oestrogen suppression was maintained throughout treatment in all these patients.

Letrozole is specific in inhibiting aromatase activity. Impairment of adrenal steroidogenesis has not been observed. No clinically relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxy-progesterone, and ACTH or in plasma renin activity among postmenopausal patients treated with a daily dose of letrozole, 0,1 to 5 mg. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0,1 mg, 0,25 mg, 0,5 mg, 1 mg, 2,5 mg and 5 mg did not indicate any attenuation of aldosterone or cortisol production. Thus, glucocorticoid and mineralocorticoid supplementation are not necessary.

No changes were noted in plasma concentrations of androgens (androstenedione and testosterone) among healthy postmenopausal women after 0,1 mg; 0,5 mg and 2,5 mg single doses of letrozole or in plasma concentrations of androstenedione among postmenopausal patients treated with daily doses of 0,1 to 5 mg, indicating that the blockade of oestrogen biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of LH and FSH are not affected by letrozole in patients, nor is thyroid function as evaluated by TSH, T4 and T3 uptake.

5.2 Pharmacokinetic properties

Absorption:

Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99,9 %). Food slightly decreases the rate of absorption, but the extent of

absorption (AUC) is not changed. The minor effect on the absorption rate is not considered to be of clinical relevance and therefore letrozole may be taken without regard to mealtimes.

Distribution:

Plasma protein binding of letrozole is approximately 60 %, mainly to albumin (55 %). The concentration of letrozole in erythrocytes is about 80 % of that in plasma. After administration of 2,5 mg 14C-Iabelled letrozole, approximately 82 % of the radioactivity in plasma was unchanged compound. Systemic exposure to metabolites is therefore low. Letrozole is rapidly and extensively distributed to tissues. Its apparent volume of distribution at steady state is about 1,87 ± 0,47 L/kg.

Metabolism and elimination:

Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole (CL_m= 2,1 L/h) but is relatively slow when compared to hepatic blood flow (about 90 L/h). The cytochrome P450 isoenzymes 3A4 and 2A6 were found to be capable of converting letrozole to this metabolite. Formation of minor unidentified metabolites and direct renal and faecal excretion play only a minor role in the overall elimination of letrozole. Within 2 weeks after administration of 2,5 mg 14C-Iabelled letrozole to healthy postmenopausal volunteers, 88,2 ± 7,6 % of the radioactivity was recovered in urine and 3,8 ± 0,9 % in faeces. At least 75 % of the radioactivity recovered in urine up to 216 hours (84,7 ± 7,8 % of the dose) was attributed to the glucuronide of the carbinol metabolite, about 9 % to two unidentified metabolites, and 6 % to unchanged letrozole.

The apparent terminal elimination half-life in plasma is about 2 days. After daily administration of 2,5 mg steady-state levels are reached within 2 to 6 weeks. Plasma concentrations at steady state are approximately 7 times higher than concentrations measured after a single dose of 2,5 mg, while they are 1,5 to 2 times higher than the steady-state values predicted from the concentrations measured after a single dose, indicating a slight non-linearity in the pharmacokinetics of letrozole upon daily administration of 2,5 mg. Since steady-state levels are maintained over time, it can be concluded that no continuous accumulation of letrozole occurs. Age had no effect on the pharmacokinetics of letrozole.

SPECIAL POPULATIONS:

Renal impairment

In a study involving 16 postmenopausal volunteers with varying degrees of renal function (24-hour creatinine clearance 9 to 116 mL/min) no effect on the pharmacokinetics systemic exposure of letrozole was found after a single dose of 2,5 mg. In addition to the above study assessing the influence of renal impairment on letrozole, a covariate analysis was performed on the data of two pivotal studies (Study AR/BC2 and Study AR/BC3). Calculated creatinine clearance (CLcr) [Study AR/BC2 range: 10 to 180 mL/min] showed no statistically significant association between letrozole plasma trough levels at steady state (Cmin). Furthermore, data of Study AR/BC2 and Study AR/BC3 in second-line metastatic breast cancer showed no evidence of an adverse effect of letrozole on CLcr on an impairment of renal function.

Hepatic impairment

In a similar study involving subjects with varying degrees of hepatic function, the mean AUC values of the volunteers with moderate hepatic impairment (Child-Pugh score B) were 37 % higher than in normal subjects, but still within the range seen in subjects without impaired function.

In a study comparing the pharmacokinetics of letrozole after a single oral dose in eight subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh score C) to those in healthy volunteers (N=8), AUC and $t_{1/2}$ increased by 95 and 187 %, respectively. Breast cancer patients with severe hepatic impairment are thus exposed to higher levels of letrozole than patients without severe hepatic dysfunction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica, microcrystalline cellulose, lactose monohydrate, magnesium stearate, maize starch, sodium starch glycollate, hydroxypropyl-methylcellulose, polyethylene glycol 8000, talc, titanium dioxide, iron oxide yellow.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from moisture.

Keep out of reach of children.

6.5 Nature and contents of container

Blister packs of 30 tablets

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

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8. REGISTRATION NUMBER

31/21.12/0378

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

23 May 1997

10. DATE OF REVISION OF THE TEXT

05 August 2025

Namibia: 04/21.12/1408	NS2
Botswana: BOT1202226	S2

Manufacturer:

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