
SCHEDULING STATUS **S4**

PROPRIETARY NAME (AND DOSAGE FORM)

FEMARA® 2,5 Film-coated tablets

COMPOSITION

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

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.

PHARMACOLOGICAL CLASSIFICATION

A 21.12 Hormone Inhibitors.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

The elimination of estrogen-mediated stimulatory effects is a prerequisite for tumour response in cases where the growth of tumour tissue depends on the presence of estrogens. In postmenopausal women, estrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens - primarily androstenedione and testosterone - to estrone (E1) and estradiol (E2). The suppression of estrogen 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 estrone and estradiol 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 estradiol, estrone, and estrone sulphate by 75 to 95 % from baseline in all patients treated. With doses of 0,5 mg and higher, many values of estrone and estrone sulphate are below the limit of detection in the assays, indicating that higher oestrogen suppression is achieved with these doses. Estrogen 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 is 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 are thyroid function as evaluated by TSH, T4 and T3 uptake.

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-labelled 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-labelled 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:

In a study involving volunteers with varying degrees of renal function (24 hour creatinine clearance 9 to 116 ml/min) no effect on the pharmacokinetics of letrozole was found after a single dose of 2,5 mg. 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) was 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.

INDICATIONS

- Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.
- Extended adjuvant treatment of early breast cancer in post menopausal women who have received prior standard adjuvant tamoxifen therapy.
- First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer.
- Treatment of advanced breast cancer in women with natural or artificially induced postmenopausal status, who have previously been treated with antioestrogens.

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- Pre-operative therapy in postmenopausal women with localised hormone receptor positive breast cancer, to allow subsequent breast-conserving surgery in women not originally considered candidates for this type of surgery. Subsequent treatment after surgery should be in accordance with standard of care.

CONTRA-INDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- 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).

INTERACTIONS

Clinical interaction studies with cimetidine and warfarin indicated that the co-administration of FEMARA with these drugs does not result in clinically significant drug interactions.

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

There is no clinical experience to date on the use of FEMARA in combination with other anti-cancer agents. FEMARA inhibits *in vitro* the cytochrome P₄₅₀-isozymes 2A6, and moderately 2C19. CYP2A6 does not play a major role in drug metabolism.

In *in-vitro* experiments letrozole, was not able to substantially inhibit the metabolism of diazepam (a substrate of CYP2C19) at concentrations approximately 100-fold higher than those observed in plasma at steady state. Thus, clinically relevant interactions with CYP2C19 are unlikely to occur. However, caution should be used in the concomitant administration of drugs whose disposition is mainly dependent on these isoenzymes and whose therapeutic index is narrow.

PREGNANCY AND LACTATION

FEMARA is contra-indicated during pregnancy and lactation.

DOSAGE AND DIRECTIONS FOR USE

Adults and elderly patients:

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 tumour relapse occurs, whichever comes first.

In patients with metastatic disease treatment with FEMARA should continue until tumour progression is evident.

Elderly patients:

No dose adjustment is required for elderly patients.

Children:

Not applicable.

Patients with hepatic and/or renal impairment:

No dosage adjustment is required for patients with mild to moderate hepatic impairment (Child Pugh grade A and B) or renal impairment (creatinine clearance \geq 10 ml/min.).

Insufficient data are available to establish dosage recommendations for patients with a creatinine clearance of < 10 ml/min (see contra-indications).

However, FEMARA should not be used in patients with severe hepatic impairment (Child-Pugh score C).

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

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 40 % of the patients in the extended adjuvant setting (both FEMARA and placebo arms) can be expected to experience adverse reactions.

In the metastatic and neoadjuvant settings, the most frequently reported adverse reactions in the clinical trials were hot flushes (10.8 %), nausea (6.9 %) and fatigue (5.0 %). Many adverse reactions can be attributed to the normal pharmacological consequences of oestrogen deprivation (e.g. hot flushes, alopecia and vaginal bleeding).

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.

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 isolated reports.

Infections and infestations Uncommon	Urinary tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps) Uncommon	Tumour pain ⁶⁾
Blood and the lymphatic system disorders Uncommon	Leukopenia
Metabolism and nutrition disorders Common Uncommon	Anorexia, appetite increase, hypercholesterolemia General oedema
Psychiatric disorders Common Uncommon	Depression, Anxiety ¹⁾
Nervous system disorders Common Uncommon	Headache, dizziness Somnolence, insomnia, memory impairment, dysaesthesia ²⁾ , taste disturbance, cerebrovascular accident
Eye disorders Uncommon	Cataract, eye irritation, blurred vision
Cardiac disorders Uncommon	Palpitations, tachycardia
Vascular disorders Uncommon Rare	Thrombophlebitis ³⁾ , hypertension, ischemic cardiac events ⁷⁾ Pulmonary embolism, arterial thrombosis, cerebrovascular infarction
Respiratory, thoracic and mediastinal disorders Uncommon	Dyspnoea
Gastrointestinal disorders Common Uncommon	Nausea, vomiting, dyspepsia, constipation, diarrhoea Abdominal pain, stomatitis, dry mouth
Hepato-biliary disorders Uncommon	Increased hepatic enzymes
Skin and subcutaneous tissue disorders Common Uncommon	Alopecia, increased sweating, rash ⁴⁾ Pruritus, dry skin, urticaria
Musculoskeletal, connective tissue and bone disorders Very common Common Uncommon	Arthralgia Myalgia, bone pain, osteoporosis, bone fractures. Arthritis,
Renal and urinary disorders Uncommon	Increased urinary frequency.

Reproductive system and breast disorders Uncommon	Vaginal bleeding, vaginal discharge, vaginal dryness, breast pain
General disorders and administration site conditions Very common Common Uncommon	Hot flushes Fatigue ⁵⁾ , peripheral oedema Pyrexia, mucosal dryness, thirst
Investigations Common Uncommon	Weight increase Weight loss

***Including:**

- (1) including nervousness, irritability
- (2) including paraesthesia, hypoaesthesia
- (3) including superficial and deep thrombophlebitis
- (4) including erythematous, maculopapular, psoriaform and vesicular rash
- (5) including asthenia and malaise
- (6) in metastatic/neoadjuvant setting only
- (7) in the adjuvant setting, irrespective of causality, the following adverse events occurred in the FEMARA and tamoxifen groups respectively: thromboembolic events (1.2 % vs. 2.8 %), angina pectoris (0.7 % vs. 0.6 %), myocardial infarction (0.6 % vs. 0.4 %) and cardiac failure (0.9 % vs. 0.4 %)

Impaired renal function:

FEMARA has not been investigated in patients with creatinine clearance < 10 ml/min. (See *Contra-indications*).

In patients with severe hepatic impairment (Child-Pugh score C), systemic exposure and terminal half-life were approximately doubled compared to healthy volunteers. (See *Contra-indications*).

Effects on ability to drive and use machinery:

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Isolated cases of overdosage with FEMARA have been reported. No specific treatment for overdosage is known; treatment should be symptomatic and supportive.

IDENTIFICATION

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

PRESENTATION

Blister packs of 30 tablets

STORAGE INSTRUCTIONS

Store at or below 30 °C.
Keep out of reach of children.

REGISTRATION NUMBER

31/21.12/0378

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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