

Femazol®

Letrozole

FORMS AND PRESENTATION

Femazol®: Film coated tablets: Box of 30.

COMPOSITION

Femazol®: Each film coated tablet contains Letrozole 2.5mg.

Excipients: lactose, croscarmellose sodium, povidone, colloidal silicon dioxide, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, yellow iron oxide, polyethylene glycol, talc.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic class: Endocrine therapy.

ATC code: L02BG04.

The elimination of estrogen-mediated stimulatory effects is a prerequisite for tumor response in cases where the growth of tumor 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 estrogen biosynthesis in all tissues.

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 (median t_{max} : 1 hour fasted versus 2 hours fed; and mean C_{max} : 129 ± 3 nmol/l, fasted versus 98.7 ± 18.6 nmol/l, fed) 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.

Biotransformation and elimination

Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of Letrozole (CL_{int} = 21 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 *in vitro*, but their individual contributions to Letrozole clearance *in vivo* have not been established. In an interaction study co-administration with cimetidine, which is known to inhibit only the 3A4 isoenzyme, did not result in a decrease in Letrozole clearance suggesting that *in vivo* the 2A6 isoenzyme plays an important part in total clearance. In this study a slight decrease in AUC and increase in C_{min} were observed.

Formation of minor unidentified metabolites and direct renal and fecal 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 feces. 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.

INDICATIONS

Femazol® is indicated in:

- Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.
- Treatment of early invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy.
- First-line treatment in postmenopausal women with advanced breast cancer.
- Advanced breast cancer in postmenopausal women in whom tamoxifen or other anti-estrogen therapy has failed.

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

CONTRAINDICATIONS

- Known hypersensitivity to the active substance or to any of the excipients.
- Premenopausal, pregnant or lactating women.
- Patients with severe hepatic impairment (Child-Pugh grade C).
- Pre-operative use of Letrozole is contraindicated if the receptor status is negative or unknown.

PRECAUTIONS

Letrozole is not recommended for use in children as efficacy and safety in this patient group have not been assessed in clinical studies. There are no efficacy data to support the use of Letrozole in men with breast cancer.

Letrozole has not been investigated in patients with creatinine clearance < 10 mL/min. The potential risk/benefit to such patients should be carefully considered before administration of Letrozole.

As Letrozole is a potent estrogen lowering agent, reductions in bone mineral density can be anticipated. During adjuvant treatment with Letrozole, women with osteoporosis or at risk of osteoporosis should receive their bone mineral density formally assessed by bone densitometry e.g. DEXA scanning at the commencement of treatment. Treatment for osteoporosis should be initiated as appropriate and patients treated with Letrozole should be carefully monitored.

Ability to drive and use machines

Since fatigue and dizziness have been observed with the use of Letrozole and somnolence has been reported uncommonly, caution is advised when driving or using machines.

PREGNANCY AND LACTATION

Letrozole is contraindicated during pregnancy.

Isolated cases of birth defects (labial fusion, ambiguous genitalia) have been reported in pregnant women exposed to Letrozole.

Letrozole is contraindicated during lactation.

The physician needs to discuss the necessity of adequate contraception with women who have the potential to become pregnant including women who are peri-menopausal or who have recently become postmenopausal, until their postmenopausal status is fully established.

There are no adequate data from the use of Letrozole in pregnant women.

Studies in animals have shown reproductive toxicity.

DRUG INTERACTIONS

Clinical interaction studies with cimetidine and warfarin indicated that the co-administration of Letrozole with these drugs does not result in clinically significant drug interactions, even though cimetidine is a known inhibitor of one of the cytochrome P450 isoenzymes capable of metabolizing Letrozole *in vitro*. There was no evidence of other 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 Letrozole in combination with other anti-cancer agents.

Letrozole inhibits *in vitro* the cytochrome P450-isoenzymes 2A6 and moderately 2C19; however, 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. Nevertheless, caution should be used in the concomitant administration of drugs whose disposition is mainly dependent on these isoenzymes and whose therapeutic index is narrow.

ADVERSE EFFECTS

Letrozole 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 as well as in the treatment of women who have received prior standard tamoxifen therapy. Approximately one third of the patients treated with Letrozole in the metastatic and neoadjuvant settings, and approximately 80% of the patients in the adjuvant setting (both Letrozole and tamoxifen arms, at a median treatment duration of 60 months), and approximately 80% of the patients treated following standard adjuvant tamoxifen (both Letrozole and placebo arms, at a median treatment duration of 60 months) experienced adverse reactions. Generally, the observed adverse reactions are mainly mild or moderate in nature, and most are associated with estrogen deprivation.

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

The following adverse drug reactions were reported from clinical studies and from post marketing experience with Letrozole.

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%); not known (cannot be estimated from the available data).

- Infections and infestations: Urinary tract infection (uncommon).
- Neoplasms, benign, malignant and unspecified (including cysts and polyps): Tumor pain in metastatic/neoadjuvant setting only (uncommon).
- Blood and the lymphatic system disorders: Leucopenia (uncommon).
- Immune system disorders: Angioedema, anaphylactic reactions (not known).
- Metabolism and nutrition disorders: Anorexia, appetite increase, raised serum cholesterol (common); general edema (uncommon).
- Psychiatric disorders: Depression (common); anxiety including nervousness, and irritability (uncommon).
- Nervous system disorders: Headache, dizziness (common); somnolence, insomnia, memory impairment, dysclexia including paresthesia and hypoesthesia, taste disturbance, cerebrovascular accident, carpal tunnel syndrome (uncommon).
- Eye disorders: Cataract, eye irritation, blurred vision (uncommon).
- Cardiac disorders: Palpitations, tachycardia (uncommon).
- Vascular disorders: Thrombophlebitis including superficial and deep thrombophlebitis, hypertension, ischemic cardiac events (uncommon); pulmonary embolism, arterial thrombosis, cerebrovascular infarction (rare).
- Respiratory, thoracic and mediastinal disorders: Dyspnea, cough (uncommon).
- Gastrointestinal disorders: Nausea, vomiting, dyspepsia, constipation, diarrhea (common); abdominal pain, stomatitis, dry mouth (uncommon).
- Hepatobiliary disorders: Increased hepatic enzymes (uncommon); hepatitis (not known).
- Skin and subcutaneous tissue disorders: Alopecia, increased sweating, rash including erythematous, maculopapular, psoriasisform and vesicular rash (common); pruritus, dry skin, urticaria (uncommon); toxic epidermal necrolysis, erythema multiforme (not known).
- Musculoskeletal and connective tissue disorders: Arthralgia (very common); myalgia, bone pain, osteoporosis, bone fractures (common); arthritis (uncommon); trigger finger (not known).
- Renal and urinary disorders: Increased urinary frequency (uncommon).
- Reproductive system and breast disorders: Vaginal bleeding, vaginal discharge, vaginal dryness, breast pain (uncommon).
- General disorders and administration site conditions: Hot flushes (very common); fatigue including asthenia and malaise, peripheral edema (common); pyrexia, mucosal dryness, thirst (uncommon).
- Investigations: Weight increase (common); weight loss (uncommon).

DOSEAGE AND ADMINISTRATION

Adult and elderly patients

The recommended dose of Femazol® is 2.5 mg once daily. In the adjuvant setting, treatment with Femazol® should continue for 5 years or until tumor relapse occurs, whichever comes first. Following standard adjuvant tamoxifen therapy, treatment with Femazol® should continue for 5 years or until tumor relapse occurs, whichever comes first. In patients with metastatic disease, treatment with Femazol® should continue until tumor progression is evident. Regular monitoring to observe progression during the pre-operative treatment period is recommended. No dose adjustment is required for elderly patients.

Children

Not recommended for use in children.

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 ≥ 10 mL/min).

OVERDOSE

There is no clinical experience of overdose. In animal studies, Letrozole exhibits only a slight degree of acute toxicity. In clinical trials, the highest single and multiple doses tested in healthy volunteers was 30 mg and 5 mg, respectively, the latter also being the highest dose tested in postmenopausal breast cancer patients. Each of these doses was well tolerated. There is no clinical evidence for a particular dose of Letrozole resulting in life-threatening symptoms.

There is no specific antidote to Letrozole. In general, supportive care, symptomatic treatment and frequent monitoring of vital signs are appropriate.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

Date of revision: August 2016.

This is a medication
- A medication is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medication.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Medication: keep out of reach of children.
Source of Arab Health Media
Council of Arab Pharmaceutical

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بيّنت الدراسات السد

في محور أي اتجاه يبروزة (تدعى بـتحيز) عند استخدام الترددات الزاوية من 0 إلى 2000 هرتز. معالجة الصور
 باستخدام الترددات الزاوية في المحور الخلفي في المحترق نظري التردد المستطوي. P_{max} و ٢٨١ وشكل سطح التردد
 C_{191} في المحور الخلفي في المحترق نظري التردد المستطوي. يودي هذا أساسيا في استغلال الخوار في إطار التردد المستطوي، لم يتمكن
 الترددات الزاوية من أن يغطي بشكل جيد في المحترق نظري التردد المستطوي (أشكال ٢٨٢ و ٢٨٣). عندما تكون الترددات الزاوية أكبر
 من ٢٠٠ هرتز، كلما تزايدت قيم الترددات الزاوية، كلما تزايدت قيم الترددات الزاوية. في المستطوي (CVC) في أوقات طويلة من الشريحة
 السريعة من البروتين CVC_{191} ، لكي نجيح عند أخذ الصور هذا من الترددات الزاوية من الترددات الزاوية عندما تكون
 قيمها أكبر من القيمة عند الترددات الزاوية (أشكال ٢٨٤ و ٢٨٥) عندما تكون صور هذا المعالجين.

تَبَيَّنَ مِنْ خِلَالِ كُلِّ

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الاستمرارية النفسية، والسياسية، الدينية، الاجتماعية، الاقتصادية، الثقافية، والبيئية (غير شائع).
 اضطراب الجهاز العصبي: ضجاع (خوف شائع)، نباح، أرق، خلل في الذاكرة، خلل في الإحساس ويشمل المذل
 ونقص الجن، خلل في حاسة الذوق، حادثة وعائية دماغية (سكتة) وملازمة النفق الرعشي (غير شائع).
 اضطراب ألبت بصري: ساد (اعتماد عديمة العین)، نهج في العين، تنوُّش الرؤية (غير شائع).
 اضطراب ألبت قلبي: خفجان، القلب، تسرع عقدة القلب (غير شائع).

اضطرابات كبدية صفراوية: تزداد الإنزيمات الكبدية (غير شائع)، التهاب الكبد (غير معلوم).
 اضطرابات في الجلد والتسبج تحت الجلد: تغلّبة (صلع)، تفرّج متزايد، طفرة وتشمّل حالات الطفرة الحامضية، البقع، الخطاطية، الصدفية الشكل (والحموضة شائعة)، جفاف البشرة، شرى (غير شائع)، تقشر الأنسجة المتوترة البشرية (غير شائع).
 تشنّجى، حملى غديّة الأشكال (غير معلوم).

عند المرضى البالغين و المسنين
إن الجرعة الموصى بها من الفينازول® هي ٢,٥ ملغ مرة في اليوم. عند تلقي معالجة مساعدة، يجب أن يستمر العلاج بالفينازول® لمدة خمس سنوات أو لحين حصول التكاثر، أيهما سبق. بعد تلقي المعالجة المساعدة المعتمدة عادةً

لا يُنصح باستعمال هذا الدواء عند الأولاد.
 عند المرضى المصابين بقصور كبدى و/أو كلوي
 لا تدعو الحاجة إلى تكيف الجرعات عند المرضى
 المصابين بقصور كبدى خفيف إلى متوسط الحدة (من النمط A و B)

المريضات حوامل جدد، مريضات الجذع عظيم. لا تتوافر أي براهين على الصعید السريزي نود على أن جرعة محددة من الليترزول تنسب أعراض هذه الحالة.

لا تتوافر أي تریاقات خاصة بمعالجة حالات تناول جرعة مفرطة من الليترزول. من المستحسن عامة تأمين عناية داعمة، ومراقبة الأعراض، ومراقبة العلامات الحيوية بشكل منتظم.

ملاحظة: حفظ الدواء

تاريخ مراجعة هذه المشرة : آذار ٢٠١٤ .

- النواء مستحضر يؤثر على صحتك، وإستهلاكه خلافاً للتعليمات يعرضك للخطر.

- إتبع وصفة الطبيب بدقة، وإرشادات الإستعمال، وتعليمات الصيدلاني الذي صرفها لك.

بنی ش.م.ل.
ضبیہ - لبنان

التركيب
 فيمازول®: يحتوي كل قرص من فيمازول® المغطى بالغيليم على ٢٠٥ ملغ من الليتوزول.
 المواد غير الفعالة: لكتوز، كروس كارميلوز الصوديوم، بوفيتون، ثاني أكسيد السيليكون الغروي، إبيتيرات المغنيزيوم، هيدروكسي بروبيل ميثيل السيللوز، ثاني أكسيد التيتانيوم، أصفر أكسيد الحديد، بولي إيثيلين غليكول، طلق.

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٩٨٠,٧ ± ١٨٧,٦ ناومول في اللتر بعد تناول الطعام) لكن لا يطرأ أي تعديل على مدى الامتصاص (المصاحبة تحت منحني التكريز). أما التأثير الطفيف على الامتصاص فلا قيمة له من الناحية السريرية وبالتالي يمكن تناول الليتوزول مع الطعام أو بدونه.

يشكل التصريف الاستقلابي لمُسْتَقْبَل الكاربينول غير النشط من الناحية الصيدلانية مسار التصريف الأساسي للـ ليتوزول (تصريف المُسْتَقْبَل = ١,٦ لتر في الساعة) لكنه بطيء نسبياً عندما تَمرّ قنطرة مع سرعة تدفق الدم إلى الكبد (حوالي ٩٠ لتر في الساعة).

يوضح في إطار هذه الدراسة انخفاض طيفي في المساحة تحت منحنى التردد ويراد به نسبة التردد القصوى (C_{max}) للعلامة تكون مسطبات صغيرة و غير محددة الهوية والإفراز المباشر عبر الكلىتين و البراز دورًا ثانوي في التصريف (C_{max}) للأدوية. في خلال الأسابيع بين صفر نصف التوزيع الموسوم بالبولون ١ المصنوع إلى منقطة على جملة صحية جيدة بلغت مرحلة ما بعد انقطاع الطمث، تم استرجاع نسبة $88.2 \pm 7.1\%$ من المنة من النشاط الإشعاعي في البول و $3.8 \pm 0.2\%$ في البراز.

لا يؤثر عمر المريض على حركات الليتورزول الدوائية.

دواعي الاستعمال

يوصف فيمازول® في الحالات التالية :

• معالجة مساعدة للنساء في مرحلة ما بعد انقطاع الطمث عند إصابتهن بسرطان الثدي الإجتياحي والإيجابي الاستجابة

علاج حب الشباب في مرحلة ما بعد انقطاع الطمث عند إصابتهن بترنص ممتد في السدي والعلاج بتدليك مسطرين

• عند المرضى المصابين بقصور كبدي حاد (من النمط C بحسب تصنيف Child-Pugh)، يُحظر استخدام الليتورزول قبل إجراء العملية الجراحية عندما يكون مستقبل الهرمون سليماً أو مجهولاً.

ويجب مراقبة المرضى الذين يخضعون لعلاج بالليزر وروى عن حب.
القدرة على قيادة المركبات وتشغيل الآلات
بما أنه لوحظ أن المرضى الخاضعين لعلاج بالليزر وزول أصيبوا بالتعب والدوخة وبما أن التعاس من تأثيراته الجانبية غير
الشفاعة، يجب توخي الحذر عند قيادة المركبات وتشغيل الآلات.

على الطبيب أن يناقش موضوع الجوء الضروري إلى وسائل منع الحمل المناسبة مع النساء في سن الإنجاب بما فيهن النساء في الفترة المحيطة بسن اليأس أو اللواتي بلغن مرحلة ما بعد انقطاع الطمث حتى تنقطع دورتهن الشهرية بشكل نهائي. لا تُؤثر معطيات مناسبة حول استخدام الفيتروزال عند النساء الحوامل.

غير أن الدراسات عند الحيوانات قد أظهرت أن انتقال السمعة التناسلية
