FEMARA®

(letrozole)

2.5 mg Film-coated Tablets

LEAFLET

DISETUJUI OLEH BPOM: 04/10/2021 EREG100005VR12100132

Trade name

FEMARA® 2,5 mg film-coated tablets.

Description and composition

Pharmaceutical form

Film-coated tablets.

Coated tablet, dark yellow, round, slightly biconvex with bevelled edges. One side bears the imprint “FV”, the other “CG”.

Active substance

4,4'-[(1H-1,2,4-triazol-1-yl)-methylene]bis-benzonitrile (INN/USAN= letrozole).

Each film-coated tablet contains 2.5 mg letrozole.

Excipients

Colloidal anhydrous silica, microcristalline cellulose, lactose monohydrate, magnesium stearate, maize starch, sodium starch glycollate, hydroxypropyl methylcellulose, polyethylene glycol 8000, talc, titanium dioxide (E 171), iron oxide yellow (E 172).

Clinical particulars

Therapeutic 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.
- 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 antiestrogens.
- 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.

Dosage regimen and administration

Dosage regimen

General target population

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 3 years or until tumour relapse

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occurs, whichever comes first. In patients with metastatic disease, treatment with Femara should continue until tumour progression is evident.

Special populations

Pediatric patients

Not applicable.

Hepatic impairment

No dosage adjustment of Femara is required for patients with hepatic impairment.

Renal impairment

No dosage adjustment of Femara is required for patients with renal impairment (creatinine clearance ≥10 mL/min).

Geriatric patients (65 years of age or older)

No dose adjustment is required for elderly patients.

Method of administration

Femara should be taken orally and can be taken with or without food because food has no effect on the extent of absorption.

Missed dose

The 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 her regular dosage schedule. Doses should not be doubled because with daily doses over the 2.5 mg recommended dose, over-proportionality in systemic exposure was observed (see section Clinical pharmacology).

Contraindications

- Known hypersensitivity to the active substance or to any of the excipients. Premenopausal endocrine status; pregnancy, lactation (see sections Pregnancy, lactation and females and males of reproductive potential and Non-clinical safety data).
- Patients with severe hepatic impairment (child-plug grade C).

Warnings and precautions

Renal impairment

Femara 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 Femara.

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Hepatic impairment

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

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 (see sections Adverse drug reactions and Pharmacodynamics).

Menopausal status

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

Fertility

The pharmacological action of letrozole is to reduce estrogen production by aromatase inhibition. In premenopausal women, the inhibition of estrogen 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-estrogens or estrogen-containing therapies should be avoided as these substances may diminish the pharmacological action of letrozole. The mechanism of this interaction is unknown (see section Interactions).

Driving and using machines

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

Interactions

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

Drugs that may increase Letrozole serum concentrations

Inhibitors of CYP3A4 and CYP2A6 activities could decrease the metabolism of letrozole and thereby increase plasma concentrations of letrozole. The concomitant administration of medications that strongly inhibit 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 letrozole. Therefore

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caution is recommended in patients for whom strong CYP3A4 and CYP2A6 inhibitors are administered.

Drugs that may decrease Letrozole serum concentrations

Inducers of CYP3A4 activity could increase the metabolism of letrozole and thereby decrease plasma concentrations of letrozole. The concomitant administration of medications that induce CYP3A4 (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital, and St. John's Wort) may reduce exposure to letrozole. Therefore caution is recommended in patients for whom strong CYP3A4 inducers are administered. No drug inducer is known for CYP2A6

Co-administration of Femara (2.5mg) and tamoxifen 20 mg daily resulted in a reduction of letrozole 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.

Drugs that may have their systemic serum concentrations altered by Letrozole

In vitro, letrozole inhibits the cytochrome P450 isoenzymes CYP2A6 and, moderately, CYP2C19, but the clinical relevance is unknown. Caution is therefore indicated when giving letrozole concomitantly with medicinal products whose elimination is mainly dependent on CYP2C19 and whose therapeutic index is narrow (e.g. phenytoin, clopidogrel). No substrate with a 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 a narrow therapeutic window and commonly used as co-medication in the target population of letrozole) indicated that the coadministration of Femara with these drugs does not result in clinically significant drug interactions.

A review of the clinical trial database indicated no evidence of other clinically relevant interaction with other commonly prescribed drugs.

Pregnancy, lactation, females and males of reproductive potential

1. Pregnancy

Risk summary

Femara is contraindicated in women who are pregnant [see section Contraindications]. Femara may cause fetal harm when administered to a pregnant woman. The patient should be apprised of the potential risk to the fetus, if Femara is used during pregnancy or if the patient becomes pregnant while taking this drug.

There are no clinical trials conducted in pregnant women with Femara. However, there are post-marketing reports of spontaneous abortions and congenital anomalies in infants of mothers who took Femara (see section Warnings and precautions) during pregnancy. Reproductive toxicity studies in rats demonstrated Femara induced embryotoxicity and fetotoxicity as well as teratogenicity. Femara caused adverse pregnancy outcomes, including congenital malformations, in rats and rabbits at doses much smaller than the daily maximum recommended human dose (MHRD) on a mg/m^2 basis. Observed effects included increased

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post-implantation pregnancy loss and resorptions, fewer live fetuses, and fetal malformations affecting the renal and skeletal systems.

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

Animal Data

In embryo-fetal development studies, pregnant rats received oral doses of Femara up to 0.03 mg/kg/day during the period of organogenesis. Reproduction studies in rats showed embryotoxicity and fetotoxicity at letrozole doses ≥ 0.003 mg/kg during organogenesis which is equal to or greater than 1/100 the MHRD (mg/m^2 basis). Embryo-and fetotoxic effects observed at doses ≥ 0.003 mg/kg included intrauterine mortality, increased resorption, increased post-implantation loss, decreased number of live fetuses and fetal anomalies including shortening of renal papilla, dilation of ureter, edema and skeletal variations. Letrozole doses of 0.03 mg/kg which is 1/10 the MHRD (mg/m^2 basis) were teratogenic and caused fetal domed head and cervical/centrum vertebral fusion.

In the embryo-fetal development study in pregnant rabbits, oral administration of letrozole was associated with signs of embryotoxicity and fetotoxicity at doses ≥ 0.006 mg/kg/day, as indicated by increased resorption, increased postimplantation loss and decreased numbers of live fetuses. There was no evidence of teratogenicity.

2. Lactation

Risk summary

Femara is contraindicated during lactation (see section Contraindications).

It is not known if letrozole 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. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from Femara, a nursing woman should be advised on the potential risks to the child. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Femara and any potential adverse effects on the breast-fed child from Femara or from the underlying maternal condition.

Data

Animal data

Exposure of lactating rats to letrozole was associated with an impaired reproductive performance of the male offspring at a letrozole dose as low as 0.003 mg/kg/day. There were no effects on the reproductive performance of female offspring.

3. Females and males of reproductive potential

Contraception

The physician 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.

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Females of reproductive potential should be advised that human data and animal studies have shown Femara to be harmful to the developing fetus. Sexually-active females of reproductive potential should use effective contraception (methods that result in less than 1 % pregnancy rates) when using Femara during treatment and for *20 days* (5 x T½) after stopping treatment with Femara.

Infertility

Fertility studies in rats showed that letrozole has adverse effects on male and female fertility at doses relevant to man. Exposure of letrozole to lactating rats was associated with an impaired reproductive performance of the male offspring at a letrozole dose as low as 0.003 mg/kg/day. There were no effects on the reproductive performance of female offspring.

In a juvenile rat study, decreased fertility at all doses (lowest dose at 0.003 mg/kg/day) was accompanied by hypertrophy of the hypophysis, testicular changes which included a degeneration of the seminiferous tubular epithelium and atrophy of the female reproductive tract. With the exception of bone size in females and morphological changes in the testes, all effects were at least partially reversible. Based on animal studies, Femara may impair fertility in males of reproductive potential.

Adverse drug reactions

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 adjuvant therapy with tamoxifen. Approximately one third of the patients treated with Femara in the metastatic and neoadjuvant settings, approximately 81% of the patients in the adjuvant setting (in both Femara and tamoxifen arms), 87-88% of the patients in the sequential treatment arms, at a median treatment duration of 60 months and approximately 80% of the patients in the extended adjuvant setting (both Femara 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 many are associated with oestrogen 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 oestrogen deprivation (e.g. hot flushes, alopecia and vaginal bleeding). 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 from post marketing experience with Femara

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).

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Table -1 Adverse drug reactions

Infections and infestations	
Uncommon	Urinary tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	Tumour pain[1)]
Blood and the lymphatic system disorders	
Uncommon	Leukopenia
Immune system disorders	
Not known	Anaphylatic reaction
Metabolism and nutrition disorders	
Very common	Hypercholesterolemia
Common	Decreased appetite, increased appetite
Uncommon	General oedema
Psychiatric disorders	
Common	Depression
Uncommon	Anxiety (including nervousness), irritability
Nervous system disorders	
Common	Headache, dizziness, vertigo
Uncommon	Somnolence, insomnia, memory impairment, dysaesthesia (including paraesthesia, hypoaesthesia), dysgeusia, cerebrovascular accident, carpal tunnel syndrome
Eye disorders	
Uncommon	Cataract, eye irritation, blurred vision
Cardiac disorders	
Common	Palpitations
Uncommon	Tachycardia, ischemic cardiac events (including new or worsening angina, angina requiring surgery, myocardial infarction and myocardial ischemia)
Vascular disorders	
Very common	Hot flush
Common	Hypertension
Uncommon	Thrombophlebitis (including superficial and deep vein thrombophlebitis)
Rare	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
Hepatobiliary disorders	
Uncommon	Increased hepatic enzymes, hyperbilirubinaemia, jaundice
Very rare	Hepatitis
Skin and subcutaneous tissue disorders	
Very common	Hyperhydrosis
Common	Alopecia, dry skin, rash (including erythematous, maculopapular, psoriaform, and vesicular rash)
Uncommon	Pruritus, urticaria
Very rare	Angioedema, toxic epidermal necrolysis, erythema multiforme

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Musculoskeletal and connective tissue disorders	
Very common	Arthralgia
Common	Myalgia, bone pain, osteoporosis, bone fractures, arthritis, back pain
Renal and urinary disorders	
Uncommon	Pollakiuria
Reproductive system and breast disorders	
Common	Vaginal haemorrhage
Uncommon	Vaginal discharge, vulvovaginal dryness, breast pain
General disorders and administration site conditions	
Very common	Fatigue (including asthenia, malaise)
Common	Peripheral oedema, chest pain
Uncommon	General oedema, pyrexia, mucosal dryness, thirst
Investigations	
Common	Weight increased
Uncommon	Weight decreased
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*

Overdosage

Isolated cases of overdosage with Femara have been reported.

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

Frequent monitoring of vital signs is appropriate.

Clinical Pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Non-steroidal aromatase inhibitor (inhibitor of oestrogen biosynthesis); antineoplastic agent (ATC code L02B G04).

Mechanism of action (MOA)

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 oestrone (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.

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Letrozole is a non-steroidal aromatase inhibitor. It inhibits the aromatase enzyme by competitively binding to the haem of the cytochrome P_{450} subunit of the enzyme, resulting in a reduction of oestrogen biosynthesis in all tissues.

Pharmacodynamics (PD)

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 highly 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 is thyroid function as evaluated by TSH, T4 and T3 uptake.

Pharmacokinetics (PK)

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 ± 20.3 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 meal times.

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 ^{14}C-labelled letrozole, approximately 82% of the radioactivity in plasma was unchanged compound. Systemic exposure to metabolites is therefore low. Letrozole is rapidly

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and extensively distributed to tissues. Its apparent volume of distribution at steady state is about 1.87 ± 0.47 L/kg.

Biotransformation/ metabolism

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 P_{450} 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 ^{14}C-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.

Elimination

The apparent terminal elimination half-life in plasma is about 2 to 4 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.

Linearity/non-linearity

The pharmacokinetics of letrozole were dose proportional after single oral doses up to 10 mg (dose range: 0.01 to 30 mg) and after daily doses up to 1.0 mg (dose range: 0.1 to 5mg). After a 30 mg single oral dose there was a slightly dose over-proportional increase in AUC value. With daily doses of 2.5 and 5 mg the AUC values increased about 3.8 and 12 fold instead of 2.5 and 5 fold, respectively, when compared to the 1.0 mg/day dose. The recommended dose of 2.5 mg/day may thus be a borderline dose at which an onset of over-proportionality becomes apparent, whereas at 5 mg/day the over-proportionality is more pronounced. The dose over-proportionality is likely to be the result of a saturation of metabolic elimination processes. Steady levels were reached after 1 to 2 months at all dosage regimens tested (0.1-5.0 mg daily).

Special populations

Elderly

Age had no effect on the pharmacokinetics of letrozole.

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

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on the data of two pivotal studies (Study AR/BC2 and Study AR/BC3). Calculated creatinine clearance (CLcr) [Study AR/BC2 range: 19 to 187 mL/min; Study AR/BC3 range: 10 to 180 mL/min] showed no statistically significant association between letrozole plasma trough levels at steady-state (Cmin). Futhermore, 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 or an impairment of renal function.

Therefore, no dose adjustment is required for patients with renal impairment (CLcr ≥10 mL/min). Little information is available in patients with severe impairment of renal function (CLcr <10 mL/min).

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) 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 expected to be exposed to higher levels of letrozole than patients without severe hepatic dysfunction. However, since in patients dosed at 5 or 10 mg/day no increase in toxicity was observed, a dose reduction in patients with severe hepatic impairment appears not to be warranted, although such patients should be kept under close supervision. In addition, in two well-controlled studies involving 359 patients with advanced breast cancer, no effect of renal impairment (calculated creatinine clearance: 20 to 50 mL/min) or hepatic dysfunction was found on the letrozole concentration.

Clinical studies

Adjuvant treatment

Study BIG 1-98 (CFEM345 0019)

BIG-98 is a multicenter, double-blind study which randomized over 8,000 postmenopausal women with resected receptor-positive early breast cancer, to one of the following arms:

- A. tamoxifen for 5 years
- B. Femara for 5 years
- C. tamoxifen for 2 years followed by Femara for 3 years
- D. Femara for 2 years followed by tamoxifen for 3 years

This study was designed to investigate two primary questions: whether Femara for 5 years was superior to tamoxifen for 5 years (Primary Core Analysis and Monotherapy Arms Analysis) and whether switching endocrine treatments at 2 years was superior to continuing the same agent for a total of 5 years (Sequential Treatments Analysis).

The primary endpoint was disease free survival (DFS), secondary endpoints were overall survival (OS), distant disease free survival (DDFS), systemic disease-free survival (SDFS), invasive contralateral breast cancer, and time to distant metastasis (TDM).

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Efficacy results at a median follow-up of 26 months and 60 months

Data in Tables 2 reflects result of the Primary Core Analysis based on data from the monotherapy arms (A and B) and from the two switching arms (C and D) at a median treatment duration of 24 months and a median follow-up of 26 months and at a median treatment duration of 32 months and a median follow-up of 60 months.

The 5-year DFS rates were 84% for Femara and 81.4% for tamoxifen.

Table 2 **Primary Core Analysis: Disease-free and overall survival, at a median follow-up of 26 months and at median follow-up of 60 months (ITT population)**

	Primary Core Analysis					
	Median follow-up 26 months			Median follow-up 60 months		
	Femara N=4003	Tamoxifen N=4007	HR[1] (95% CI) *p*	Femara N=4003	Tamoxifen N=4007	HR[1] (95% CI) *p*
Disease-free survival events[2]	351	428	0.81 (0.70, 0.93) 0.003	585	664	0.86 (0.77, 0.96) 0.008
Overall survival[3]	166	192	0.86 (0.70, 1.06)	330	374	0.87 (0.75, 1.01)

HR = Hazard ratio; CI = Confidence interval

[1] *Log rank test, stratified by randomisation option and use of chemotherapy (yes/no)*

[2] *DFS events: loco-regional recurrence, distant metastasis, invasive contralateral breast cancer, second (non-breast) primary malignancy, death from any cause without a prior cancer event.*

[3] *Number of deaths*

Results at a median follow-up of 96 months (monotherapy arms only)

The Monotherapy Arms Analysis long-term update of the efficacy of Femara monotherapy compared to tamoxifen monotherapy (median duration of adjuvant treatment: 5 years) is presented in Table 3.

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Table 3 **Monotherapy Arms Analysis: Disease-free and overall survival at a median follow-up of 96 months (ITT population)**

	Femara N=2463	Tamoxifen N=2459	Hazard Ratio[1] (95% CI)	P Value
Disease-free survival events[2]	626	698	0.87 (0.78, 0.97)	0.01
Time to distant metastasis	301	342	0.86 (0.74, 1.01)	0.06
Overall survival[3]	393	436	0.89 (0.77, 1.02)	0.08
Censored analysis of DFS[4]	626	649	0.83 (0.74, 0.92)	
Censored analysis of OS[4]	393	419	0.81 (0.70, 0.93)	

[1] Log rank test, stratified by randomization option and use of chemotherapy (yes/no)

[2] DFS events: loco-regional recurrence, distant metastasis, invasive contralateral breast cancer, second (non-breast) primary malignancy, death from any cause without a prior cancer event.

[3] Number of deaths

[4] Observations in the tamoxifen arm censored at the date of selectively switching to letrozole after tamoxifen arm was unblinded

Sequential Treatments Analysis

The Sequential Treatments Analysis (STA) addresses the second primary question of BIG 1-98, namely whether sequencing of tamoxifen and letrozole would be superior to monotherapy. There were no significant differences in DFS, OS, SDFS, or DDFS from switch with respect to monotherapy (Table 4).

Table 4 **Sequential treatments analysis of disease-free survival with letrozole as initial endocrine agent (STA switch population)**

	N	Number of events[1]	Hazard ratio[2]	(97.5% confidence interval)	Cox model P-value
[Letrozole→]Tamoxifen	1,460	254	1.03	(0.84, 1.26)	0.72
Letrozole	1,463	249			

[1] Protocol definition, including second non-breast primary malignancies, after switch / beyond two years

[2] Adjusted by chemotherapy use

There were no significant differences in DFS, OS, SDFS or DDFS in any of the STA from randomization pairwise comparisons (Table 5).

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Table 5 Sequential Treatments Analyses from randomization (STA-R) of disease-free survival (ITT STA-R population)

	Letrozole → Tamoxifen	**Letrozole**
Number of patients	1,540	1,546
Number of patients with DFS events (protocol definition)	330	319
Hazard ratio[1] (99% CI)	1.04 (0.85, 1.27)	
	Letrozole → Tamoxifen	**Tamoxifen[2]**
Number of patients	1,540	1,548
Number of patients with DFS events (protocol definition)	330	353
Hazard ratio[1] (99% CI)	0.92 (0.75, 1.12)	

[1] *Adjusted by chemotherapy use (yes/no)*

[2] *626 (40%) patients selectively crossed to letrozole after tamoxifen arm unblinded in 2005*

The following tables 6 and 7 provide information on significant differences in Femara versus tamoxifen monotherapy and in the Femara-tamoxifen sequential treatment therapy:

Table 6 Adjuvant Femara monotherapy versus tamoxifen monotherapy – adverse events with significant differences

	Femara N=2448		**Tamoxifen N=2447**	
	During treatment (median 5 years)	**Any time after randomization (median 96 months)**	**During treatment (median 5 years)**	**Any time after randomization (median 96 months)**
Bone fracture	10.2%	14.7%	7.2%	11.4%
Osteoporosis	5.1%	5.1%	2.7%	2.7%
Thromboembolic events	2.1%	3.2%	3.6%	4.6%
Myocardial infarction	1.0%	1.7%	0.5%	1.1%
Endometrial hyperplasia / endometrial cancer	0.2%	0.4%	2.3%	2.9%
Note: Median duration of treatment 60 months. Reporting period includes treatment period plus 30 days after stopping treatment. ”Any time after randomization” includes the follow-up period after completion or cessation of study treatment				

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Table 7 Sequential treatment versus Femara monotherapy – adverse events with significant differences

	Femara monotherapy 5 years	Femara->tamoxifen 2 years + 3 years	Tamoxifen->Femara 2 years + 3 years
	N=1535	N=1527	N=1541
Bone fractures	10.0%	7.7%*	9.7%
Endometrial proliferative disorders	0.7%	3.4%**	1.7%**
Hypercholesterolemia	52.5%	44.2%*	40.8%*
Hot flushes	37.6%	41.7%**	43.9%**
Vaginal bleeding	6.3%	9.6%**	12.7%**
* Significantly less than with Femara monotherapy **Significantly more than with Femara monotherapy Note : Reporting period is during treatment or within 30 days of stopping treatment			

Study CFEM345D2407

Study D2407 was an open-label, randomized, multicentre post-authorization safety study designed to compare the effects of adjuvant treatment with letrozole and tamoxifen on bone mineral density (BMD) and serum lipid profiles. In total, 263 patients were assigned either letrozole for 5 years (133 postmenopausal women) or tamoxifen for 2 years followed by letrozole for 3 years (130 patients). All evaluations of BMD and of serum lipids were conducted treatment-blinded in specialist central laboratories. The primary analysis of BMD and serum lipids was at 2 years.

There was a statistically significant difference between treatments at 2 years in the primary endpoint, lumbar spine (L2-L4) BMD with a median decrease of 4.1% in the letrozole arm compared to a median increase of 0.3% in the tamoxifen arm. The results for total hip BMD were similar to those for lumbar spine but less pronounced.

No patient with a normal BMD at baseline became osteoporotic during 5 years of treatment. One patient with osteopenia at baseline (T-score of -1.9) developed osteoporosis during the treatment period (assessment by central review).

Although treatment differences at the end of 5 years were attenuated such that there was no statistically significant difference between treatments in the protocol-defined clinically relevant BMD-related changes overall, there remained substantial differences in the effects of the two treatments on BMD and skeletal events. In patients with a normal T-score at baseline, significantly more patients in the letrozole arm than in the sequential treatment arm had reductions of at least 6% in lumbar spine BMD within 1 year or cumulative reductions of at least 8% over the entire treatment period. Although there was no significant difference overall between treatment arms in clinical fractures, three-quarters of the fractures in the sequential treatment arm occurred after the switch to letrozole. Both clinical fractures and impending fractures, however, tended to occur in patients whose skeletal status was compromised – i.e. patients with lower BMD T-scores at baseline, and patients with a history of fractures.

Total cholesterol levels (fasting) decreased by a median 16% in the tamoxifen arm at 6 months, and remained so for the duration of tamoxifen therapy. In the letrozole arm, total cholesterol levels were relatively stable throughout treatment. LDL cholesterol levels

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decreased in the tamoxifen arm but remained stable in the letrozole arm. Consequently, there were statistically significant differences in favour of tamoxifen in total cholesterol, LDL cholesterol and HDL: LDL ratio over the first 2 years of the study. There were no significant differences between treatments in triglycerides.

Study FACE (CFEM345D2411)

CFEM345D2411, Femara vs Anastrozole Clinical Evaluation (FACE) was an open-label, randomized, multi-center Phase IIIb study of letrozole compared with anastrozole in the adjuvant treatment of postmenopausal women with hormone receptor positive and node positive breast cancer. Randomization was stratified by lymph node status and HER-2 status. The ITT set consisted of 4,136 patients in total (2,061 who received letrozole and 2,075 assigned anastrozole). The safety set consisted of 4,111 patients (2,049 who received letrozole, and 2,062 who received anastrozole).

Median exposure to study treatment was 60 months (5 years as planned). Median follow-up was approximately 65 months. Discontinuation of treatment before 5 years occurred in 36.1% of the patients in the letrozole arm and 38.1% of those in the anastrozole arm.

The primary objective was to compare the rate of disease-free survival (DFS); the study was amended from an event-based trial to a time-based trial because of the low rate of DFS events and thus the statistical power to detect small differences in DFS between treatment arms was low. Secondary efficacy parameters were OS, time to development of distant metastases, time to development of contralateral breast cancer and distant DFS. No significant differences were observed in any efficacy endpoint. There was an estimated 7% risk reduction in recurrence in favor of letrozole (HR 0.93; 95% CI 0.80, 1.07, P=0.31). OS did not differ significantly. In the letrozole arm, 11.4% deaths occurred, compared to 11.7% in the anastrozole arm

Extended adjuvant treatment

Study MA-17 (CFEM345MA17)

In a multicenter, double-blind, randomized, placebo-controlled study (MA-17), over 5,100 postmenopausal women with receptor-positive or unknown primary breast cancer who had completed adjuvant treatment with tamoxifen (4.5 to 6 years) were randomized to either Femara or placebo for 5 years.

The primary endpoint was disease-free survival, defined as the interval between randomization and the earliest occurrence of loco-regional recurrence, distant metastasis, or contralateral breast cancer.

The first planned interim analysis at a median follow-up of around 28 months (25% of patients being followed up for at least 38 months), showed that Femara significantly reduced the risk of breast cancer recurrence by 42% compared with placebo (HR 0.58; 95% CI 0.45, 0.76; P=0.00003). The benefit in favor of letrozole was observed regardless of nodal status. There was no significant difference in overall survival: (Femara 51 deaths; placebo 62; HR 0.82; 95% CI 0.56, 1.19).

Consequently, after the first interim analysis the study was unblinded and continued in an open-label fashion: patients in the placebo arm were allowed to switch to Femara for up to 5 years. Patients who opted not to switch were followed by observation only. Over 60% of eligible patients (disease-free at unblinding) opted to switch to Femara. The final analysis included 1,551 women who switched from placebo to Femara at a median of 31 months

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(range 12 to 106 months) after completion of tamoxifen adjuvant therapy. Median duration of Femara after switch was 40 months.

The final analysis conducted at a median follow-up of 62 months confirmed the significant reduction in the risk of breast cancer recurrence with Femara.

Table 8 Disease-free and overall survival (Modified ITT population)

	Median follow-up 28 months			Median follow-up 62 months		
	Letrozole N=2582	Placebo N=2586	HR (95% CI)[2] P value	Letrozole N=2582	Placebo N=2586	HR (95% CI)[2] P value
Disease-free survival[3]						
Events	92 (3.6%)	155 (6.0%)	0.58 (0.45, 0.76) 0.00003	209 (8.1%)	286 (11.1%)	0.75 (0.63, 0.89)
4-year DFS rate	94.4%	89.8%		94.4%	91.4%	
Disease-free survival[3], including deaths from any cause						
Events	122 (4.7%)	193 (7.5%)	0.62 (0.49, 0.78)	344 (13.3%)	402 (15.5%)	0.89 (0.77, 1.03)
5 year DFS rate	90.5%	80.8%		88.8%	86.7%	
Distant metastases						
Events	57 (2.2%)	93 (3.6%)	0.61 (0.44, 0.84)	142 (5.5%)	169 (6.5%)	0.88 (0.70, 1.10)
Overall survival						
Deaths	51 (2.0%)	62 (2.4%)	0.82 (0.56, 1.19)	236 (9.1%)	232 (9.0%)	1.13 (0.95, 1.36)
Deaths[4]	- -	- -	- -	236[5] (9.1%)	170[6] (6.6%)	0.78 (0.64, 0.96)

HR = Hazard ratio; CI = Confidence Interval

[1] *When the study was unblinded in 2003, 1551 patients in the randomized placebo arm (60% of those eligible to switch – i.e. who were disease-free) switched to letrozole at a median 31 months after randomization. The analyses presented here ignore the selective crossover.*

[2] *Stratified by receptor status, nodal status and prior adjuvant chemotherapy.*

[3] *Protocol definition of disease-free survival events: loco-regional recurrence, distant metastasis or contralateral breast cancer.*

[4] *Exploratory analysis, censoring follow-up times at the date of switch (if it occurred) in the placebo arm.*

[5] *Median follow-up 62 months.*

[6] *Median follow-up until switch (if it occurred) 37 months.*

In the MA-17 bone substudy in which concomitant calcium and vitamin D were given, greater decreases in BMD compared to baseline occurred with Femara compared with placebo. The only statistically significant difference occurred at 2 years and was in total hip BMD (letrozole median decrease of 3.8% vs placebo median decrease of 2.0%).

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In the MA-17 lipid substudy there were no significant differences between letrozole and placebo in total cholesterol or in any lipid fraction.

In the updated quality of life substudy there were no significant differences between treatments in physical component summary score or mental component summary score, or in any domain score in the SF-36 scale. In the MENQOL scale, significantly more women in the Femara arm than in the placebo arm were most bothered (generally in the first year of treatment) by those symptoms deriving from estrogen deprivation – hot flushes and vaginal dryness. The symptom that bothered most patients in both treatment arms was aching muscles, with a statistically significant difference in favor of placebo.

Study MA-17R (CFEM345MA17E1)

CFEM345MA17E1 (MA-17R) was a double-blind, randomized study conducted and sponsored by the National Cancer Institute of Canada (NCIC) Clinical Trials Group (CTG) in the US and Canada, comparing letrozole to placebo in women with early breast cancer, completing five years of adjuvant aromatase inhibitor (AI) therapy either as initial therapy or after tamoxifen (including women who had participated in the MA-17 study). Randomization was stratified according to lymph node status, prior receipt of adjuvant chemotherapy, the interval between the last dose of AI therapy and randomization, and the duration of prior tamoxifen therapy. In total, 1,918 postmenopausal women were enrolled (959 patients in each treatment arm).

The median age of the patients at enrollment was 65 years. The first diagnosis of breast cancer occurred at a median 10.6 years prior to enrollment. Tamoxifen had been received for a median of 5 years prior to study enrollment, and the previous AI therapy had been received for a median duration of 5 years. Median duration of study treatment was 5 years and median follow-up was a median 6.3 years.

The primary efficacy endpoint was disease-free survival (DFS), i.e. events of breast cancer recurrence or of contralateral breast cancer, but not including deaths.

Over a median follow-up of 6.3 years, 67 DFS events occurred in the letrozole arm, 98 in the placebo arm (HR 0.66; 95% CI 0.48, 0.91, P=0.01). The risk of contralateral breast cancer was significantly reduced with letrozole compared with placebo (HR 0.42; 95% CI 0.22, 0.81; P=0.007). Overall survival was not significantly different (HR 0.97; 95% CI 0.73, 1.28; P=0.83)

Pre-operative treatment

Study CFEM345E P024

A double blind trial (P024) was conducted in 337 postmenopausal breast cancer patients randomly allocated either Femara 2.5 mg for 4 months or tamoxifen for 4 months. At baseline all patients had tumors stage T2-T4c, N0-2, M0, ER and/or PgR positive and none of the patients would have qualified for breast-conserving surgery. Based on clinical assessment there were 55% objective responses in the Femara arm versus 36% for the tamoxifen arm (P<0.001). This finding was consistently confirmed by ultrasound (Femara 35% vs tamoxifen 25%, P=0.04) and mammography (Femara 34% vs tamoxifen 16%, P<0.001). In total 45% of patients in the Femara group versus 35% of patients in the tamoxifen group (P=0.02) underwent breast-conserving therapy). During the 4-month pre-operative treatment period,

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12% of patients treated with Femara and 17% of patients treated with tamoxifen had disease progression on clinical assessment.

First-line treatment

Study CFEM345C P025

One controlled double-blind trial was conducted comparing Femara (letrozole) 2.5 mg to tamoxifen 20 mg as first-line therapy in postmenopausal women with advanced breast cancer. In 907 women, letrozole was superior to tamoxifen in time to progression (primary endpoint) and in overall objective response, time to treatment failure and clinical benefit.

The results are summarized in Table 9:

Table 9 Results at a median follow-up of 32 months

Variable	Statistic	Femara N=453	Tamoxifen N=454
Time to progression	**Median**	**9.4 months**	**6.0 months**
	(95% CI for median)	(8.9, 11.6 months)	(5.4, 6.3 months)
	Hazard ratio (HR)	0.72	
	(95% CI for HR)	(0.62, 0.83)	
		P<0.0001	
Objective response rate (ORR)	**CR+PR**	**145 (32%)**	**95 (21%)**
	(95% CI for rate)	(28, 36%)	(17, 25%)
	Odds ratio	1.78	
	(95% CI for odds ratio)	(1.32, 2.40)	
		P=0.0002	

Time to progression was significantly longer, and response rate significantly higher for letrozole irrespective of whether adjuvant anti-estrogen therapy had been given or not. Time to progression was significantly longer for letrozole irrespective of dominant site of disease. Median time to progression was 12.1 months for Femara and 6.4 months for tamoxifen in patients with soft tissue disease only and median 8.3 months for Femara and 4.6 months for tamoxifen in patients with visceral metastases.

Study design allowed patients to cross over upon progression to the other therapy or discontinue from the study. Approximately 50% of patients crossed over to the opposite treatment arm and crossover was virtually completed by 36 months. The median time to crossover was 17 months (Femara to tamoxifen) and 13 months (tamoxifen to Femara).

Femara treatment in the first-line therapy of advanced breast cancer resulted in a median overall survival of 34 months compared with 30 months for tamoxifen (logrank test P=0.53, not significant). The absence of an advantage for Femara on overall survival could be explained by the crossover design of the study.

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Second-line treatment

Two well-controlled clinical trials were conducted comparing two letrozole doses (0.5 mg and 2.5 mg) to megestrol acetate and to aminoglutethimide, respectively, in postmenopausal women with advanced breast cancer previously treated with anti-estrogens.

Study AR/BC2

Statistically significant differences were observed in favour of letrozole 2.5 mg compared to megestrol acetate in overall objective tumor response rate (24% vs 16%, P=0.04), and in time to treatment failure (P=0.04). Overall survival and time to progression was not significantly different between the 2 arms (P=0.2) and *P*=0.07, respectively).

Study AR/BC3

Letrozole 2.5 mg was statistically superior to aminoglutethimide 250 mg bd for time to progression (P=0.008), time to treatment failure (P=0.003) and overall survival (P=0.002). In this study, the response rate was not significantly different between letrozole 2.5 mg and aminoglutethimide (*P*=0.06).

Study FEM-INT-01

Study FEM-INT-01 was a large phase IIIb/IV randomized, multicenter, open-label study of letrozole 2.5 mg once daily versus anastrozole 1mg daily. Median TTP, the primary endpoint of the study, was not significantly different in the two treatment arms (approximately 6 months). Letrozole was significantly more effective than anastrozole in objective response rate (19% vs 12%, *P*=0.013).

Male breast cancer

Use of Femara in men with breast cancer has not been studied.

Non-clinical safety data

In a variety of preclinical safety studies conducted in standard animal species, there was no evidence of systemic or target organ toxicity.

Letrozole showed a low degree of acute toxicity in rodents exposed to up to 2,000 mg/kg. In dogs, letrozole caused signs of moderate toxicity at 100 mg/kg.

In repeated-dose toxicity studies in rats and dogs up to 12 months, the main findings observed can be attributed to the pharmacological action of the compound. The no-adverse effect level was 0.3 mg/kg in both species.

Oral administration of letrozole to female rats resulted in decreases in mating and pregnancy ratios and increases in pre-implantation loss.

The pharmacological effects of letrozole resulted in skeletal, neuroendocrine and reproductive findings in a juvenile rat study. Bone growth and maturation were decreased from the lowest dose (0.003 mg/kg/day) in males and increased from the lowest dose (0.003 mg/kg) in females. Bone mineral density (BMD) was also decreased at that dose in females.

Both *in vitro* and *in vivo* investigations on letrozole's mutagenic potential revealed no indications of any genotoxicity.

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In a 104-week rat carcinogenicity study, no treatment-related tumours were noted in male rats. In female rats, a reduced incidence of benign and malignant mammary tumours at all the doses of letrozole was found.

In a 104-week mouse carcinogenicity study, no treatment-related tumors were noted in male mice. In female mice, a generally dose-related increase in the incidence of benign ovarian granulosa theca cell tumors was observed at all doses of letrozole tested. These tumors were considered to be related to the pharmacological inhibition of estrogen synthesis and may be due to increased LH resulting from the decrease in circulating estrogen.

Oral administration of letrozole to gravid rats resulted in a slight increase in the incidence of fetal malformation among the animals treated. However, it was not possible to show whether this was an indirect consequence of the pharmacological properties (inhibition of oestrogen biosynthesis), or a direct effect of letrozole in its own right (see sections Contraindications and section Pregnancy, lactation, females and males of reproductive potential).

Preclinical observations were confined to those associated with the recognised pharmacological action, which is the only safety concern for human use derived from animal studies.

Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

Do not store above 30°C and do protect from moisture.

Femara should be kept out of the reach and sight of children.

Shelf-life

The expiry date is indicated on the packaging.

Nature and contents of container

PVC/PE/PVDC blister packs.

Instructions for use/handling

No specific instructions for use/handling.

Packing and Registration Number

Box of 3 blisters @ 10 film-coated tablets. Reg. No.

HARUS DENGAN RESEP DOKTER

To be dispensed only on the prescription of a physician

Manufactured by Novartis Pharma Stein AG, Stein, Switzerland for Novartis Pharma AG, Basel, Switzerland.

Packed and Released by Novartis Farma SpA, Torre Annunziata, Italy

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Imported by PT Novartis Indonesia, Jakarta, Indonesia.

CDS v.2.0 dated 15-Dec-2016, add release site information

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