NOVARTIS

Femara®

Composition
Active substance Letrozole
Excipients Tableting excipients

Pharmaceutical form and quantity of active substance per unit
2.5 mg film-coated tablets

Indications / Potential uses
Adjuvant treatment of postmenopausal women with early breast cancer (positive or unknown oestrogen or progesterone receptor status).
Adjuvant treatment of postmenopausal women with early breast cancer (positive or unknown oestrogen or progesterone receptor status) who have received 5 years of adjuvant tamoxifen therapy (extended adjuvant therapy).
Treatment of advanced breast cancer in postmenopausal women with positive oestrogen or progesterone receptor status, or with unknown receptor status, in whom postmenopausal status is natural or artificially induced.

Dosage and Administration
Adults and elderly patients
The recommended dose of Femara is 2.5 mg once daily. It may be taken with or without food (see **Absorption** under **Pharmacokinetics)**.
Adjuvant therapy with Femara should be given for 5 years, or until relapse occurs. Experience to date from clinical studies covers a period of up to 2.5 years (median) only.
Extended adjuvant therapy with Femara following 5 years of tamoxifen therapy should be continued until relapse occurs. Experience to date from clinical studies covers a period of up to 2.5 years (median) only.
In patients with advanced breast cancer, treatment should continue until tumour progression is evident.

Dosage in patients with hepatic and/or renal impairment
No dosage adjustment is necessary in patients with hepatic or renal impairment (creatinine clearance ≥10 ml/minute; see **Warnings and Precautions** and **Pharmacokinetics)**.

Paediatric use
Femara must not be given to children or adolescents.

Contraindications
Hypersensitivity to the active substance or any of the excipients.
Premenopausal endocrine status.
Pregnancy and lactation (see **Pregnancy and Lactation** and **Preclinical data**).

Warnings and Precautions
In patients whose postmenopausal status seems unclear, LH, FSH and/or oestradiol levels must be assessed before initiating treatment in order to clearly establish menopausal status.
Femara should not be given concurrently with drugs containing oestrogen because the latter would eliminate the pharmacological efficacy of Femara.
Femara reduces circulating oestrogen levels and long-term use may therefore result in a reduction in bone mineral density. In women with osteoporosis, or at risk of osteoporosis, bone density should be assessed by bone densitometry at the start of adjuvant treatment with Femara, and at regular intervals thereafter. Measures should be initiated where necessary to prevent or treat osteoporosis, and the patients in question should be closely monitored.

Renal impairment
Femara has not been investigated in women with creatinine clearance < 10 ml/minute. The benefit to such patients should be carefully weighed against the possible risks before initiation of treatment.

Hepatic impairment
In patients with severe hepatic impairment (Child-Pugh score C), systemic exposure and terminal half-life were approximately twice as high as in healthy volunteers. Such patients should therefore be closely monitored (see **Pharmacokinetics**). Clinical experience with repeated dosage is not available.

Interactions
Letrozole is a substrate of CYP3A4. While it is unlikely to have an effect on substances that are metabolized by CYP3A4, such substances could influence the biotransformation of letrozole by CYP3A4.
Letrozole inhibits CYP2A6 and, to a lesser extent, CYP2C19 *in vitro*. Caution is therefore required when concomitantly administering substances with a narrow therapeutic index whose availability is primarily dependent on these isoenzymes. CYP2A6 does not play a major role in drug metabolism. *In vitro* experiments showed that letrozole, at plasma concentrations approximately 100 times higher than those observed at steady-state, did not impair the metabolism of diazepam (a substrate of CYP2C19). Clinically relevant interactions with CYP2C19 are therefore unlikely.
Clinical interaction studies with cimetidine and warfarin showed that co-administration of Femara with these substances does not result in clinically significant drug interactions.
Concomitant administration of Femara with tamoxifen (20 mg/day) resulted in a decrease in plasma letrozole levels by 38% on average. Femara had no effect on plasma tamoxifen levels.
There is no clinical experience of the use of Femara in combination with other cytostatic agents.

Pregnancy and Lactation
Femara is contraindicated during pregnancy and lactation (see **Contraindications** and **Preclinical data**).
The physician must inform women of child-bearing potential, and women who are perimenopausal or who have recently become postmenopausal, of the necessity of adequate contraception.
There are insufficient data on use in pregnant women. Animal studies have shown evidence of reproductive toxicity (see **Preclinical data**).

Effects on ability to drive and use machines
Fatigue and dizziness have been observed in association with Femara, and there have been occasional reports of drowsiness. Caution is therefore required when driving vehicles or using machines.

Adverse effects
Adverse effects were seen in approximately 70–75% of patients receiving adjuvant treatment, and in approximately one-third of those undergoing extended adjuvant treatment or being treated for advanced breast cancer. The adverse effects reported were usually mild to moderate in nature.
The most frequently reported adverse effects in the clinical studies were hot flushes (10.9%), arthralgia (13.1%), nausea (6.9%) and fatigue (5.0%). Many adverse effects can be attributed to the consequences of oestrogen deprivation (e.g. hot flushes, hair loss and vaginal bleeding).
The following adverse effects were reported with adjuvant treatment in the Femara group and tamoxifen group, regardless whether or not there was any connection to treatment: thromboembolic events (1.2% and 3.0%), angina pectoris (0.8% and 0.8%), myocardial infarction (0.5% and 0.4%), heart failure (0.8% and 0.3%), bone fractures (6.3% and 4.7%).
The following adverse effects were observed during clinical studies and in the post-marketing phase:
Frequency estimates:
Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100),
rare (≥ 1/10 000 to < 1/1000), very rare (< 1/10 000)

Infections
Uncommon: Urinary tract infection.

Blood and lymphatic system
Uncommon: Leucopenia.

Endocrine disorders
Very common: Hot flushes (10.9%).

Metabolism and nutrition disorders
Common: Loss of appetite, increased appetite, hypercholesterolaemia, weight gain.
Uncommon: Weight loss.

Psychiatric disorders
Common: Depression.
Uncommon: anxiety, nervousness, irritability.

Nervous system disorders
Common: Headache, dizziness.
Uncommon: Drowsiness, insomnia, impairment of memory, dysaesthesias, paraesthesias, hypoaesthesias, dysgeusia.

Eye disorders
Uncommon: Cataract, eye irritation, blurred vision.

Cardiovascular system
Common: Hypertension, thromboembolism.
Uncommon: Palpitations, tachycardia, superficial and deep thrombophlebitis, hypotension, stroke, ischaemic heart disease, angina pectoris, myocardial infarction, heart failure.

Respiratory tract disorders
Uncommon: Dyspnoea, cough.

Gastrointestinal disorders
Common: Nausea, vomiting, dyspepsia, constipation, diarrhoea.
Uncommon: Abdominal pain, stomatitis, dry mouth, mucosal dryness.

Hepatobiliary disorders
Uncommon: Increased hepatic enzymes.

Skin
Common: Hair loss, increased sweating, erythematous, maculopapular, psoriasiform and vesicular skin rashes.
Uncommon: Pruritus, dry skin, urticaria.

Musculoskeletal system
Very common: Arthralgia (13.1%).
Common: Myalgia, bone pain, osteoporosis, bone fractures.
Uncommon: 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
Common: Fatigue, asthenia, malaise, peripheral oedema, generalized oedema.
Uncommon: Fever, thirst.

Overdose
Isolated cases of overdosage with Femara have been reported. No specific treatment is known. Management should be symptomatic and supportive.

Properties and Actions
ATC code: L02BG04

Mechanism of action / Pharmacodynamics
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, oestrogen is mainly derived from the action of the aromatase enzyme, which converts adrenal androgens, primarily androstenedione and testosterone, to oestrone (E_1) and oestradiol (E_2). Suppression of oestrogen biosynthesis in peripheral tissues and in the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme.
Letrozole is a selective non-steroidal aromatase inhibitor. It inhibits aromatase 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, 0.5 and 2.5mg letrozole reduce serum oestrone and oestradiol levels by 75–78% and 78%, respectively, as compared with baseline. The maximum effect is achieved within 48–78 hours.
In postmenopausal patients with advanced breast cancer, daily doses of 0.1 to 5 mg suppress plasma concentrations of oestradiol, oestrone and oestrone sulphate by 75–95% 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, indicating that higher oestrogen suppression is achieved with these doses.
Suppression of oestrogen biosynthesis was maintained throughout treatment in all cases.
Suppression of adrenal steroidogenesis has not been observed. No clinically relevant changes either in plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxy-progesterone and ACTH, or in plasma renin activity were observed in postmenopausal patients treated with daily doses of 0.1 to 5 mg letrozole. The ACTH stimulation test, performed after 6 and 12 weeks of treatment with daily doses of 0.1, 0.25, 0.5, 1, 2.5 and 5 mg, did not indicate any attenuation of aldosterone or cortisol production. Glucocorticoid and mineralocorticoid supplements are therefore not necessary.
No changes were found either in plasma concentrations of androgens (androstenedione and testosterone) in healthy postmenopausal women given single doses of 0.1, 0.5 and 2.5 mg letrozole, or in plasma concentrations of androstenedione in postmenopausal patients treated with daily doses of 0.1 to 5 mg letrozole. This indicates that inhibition of oestrogen biosynthesis does not result in accumulation of androgenic precursors. Plasma levels of LH and FSH are not adversely affected in patients using letrozole, nor is thyroid function, as evaluated by TSH, T_4 and T_3 uptake.

Clinical efficacy
Adjuvant treatment of breast cancer
In a double-blind, randomized study in over 8000 postmenopausal women with receptor-positive early breast cancer, patients were randomized to the following arms: tamoxifen vs. Femara for 5 years; tamoxifen vs. Femara for 2 years, with planned continuation of treatment for 3 years with either Femara or tamoxifen. The patients have thus far only been assessed prior to changing treatment. The median duration of treatment has been 26 months.
For the primary endpoint of the trial, disea
survival, Femara was significantly more ef
than tamoxifen (hazard ratio: 0.81; p = 0.0
95%: 0.70, 0.93). The results for 5 year di
free survival were 84% for Femara and 81
tamoxifen. With regard to the secondary e
overall survival, a total of 358 deaths were
(166 with Femara, 192 with tamoxifen). Th
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regards overall survival (hazard ratio 0.86
CI 95%: 0.70, 1.06). Patients receiving Fe
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(1.9% vs. 2.4%). The incidence of endom
cancer, in particular, was lower with Femara
with tamoxifen (0.2% vs. 0.4%).

Treatment of breast cancer following 5 adjuvant tamoxifen therapy
In a double-blind, randomized, placebo-co
study performed in 5168 postmenopausal
with primary breast cancer of positive or u
receptor status, patients who had remaine
free after completion of standard adjuvant
with tamoxifen (4.5 to 6 years) were random
to either Femara (n = 2582) or placebo (n
The final analysis conducted at the time o
ing showed that, with regard to the primar
of disease-free survival after median trea
duration of 2.5 years (25% of patients wer
for up to 38 months), Femara reduced the
recurrence by 42% compared with placeb
events 92 [3.6%] for Femara vs. 155 [6%] f
hazard ratio 0.58; p = 0.00003; CI 95%: 0
Sensitivity analysis confirmed the robustn
data. On the basis of similar results from t
analysis, the independent Data Monitoring
tee recommended unblinding the study. Th
cally significant benefit in disease-free su
favour of Femara was irrespective of noda
(node negative: hazard ratio 0.48; p = 0.0
CI 95%: 0.30, 0.78; node positive: hazard
p = 0.00168; CI 95%: 0.44, 0.83), recepto
(positive: hazard ratio 0.57; p = 0.00003;
0.44, 0.75) or prior adjuvant chemotherap
hazard ratio 0.58; p = 0.00330; CI 95%: 0
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0.84).
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For the primary endpoint of the trial, disease-free survival, Femara was significantly more effective than tamoxifen (hazard ratio: 0.81; p = 0.003; CI 95%: 0.70, 0.93). The results for 5 year disease-free survival were 84% for Femara and 81.4% for tamoxifen. With regard to the secondary endpoint, overall survival, a total of 358 deaths were reported (166 with Femara, 192 with tamoxifen). There was no significant difference between the two treatments as regards overall survival (hazard ratio 0.86; p = 0.15; CI 95%: 0.70, 1.06). Patients receiving Femara had fewer secondary malignancies than those on tamoxifen (1.9% vs. 2.4%). The incidence of endometrial cancer, in particular, was lower with Femara than with tamoxifen (0.2% vs. 0.4%).

Treatment of breast cancer following 5-year adjuvant tamoxifen therapy

In a double-blind, randomized, placebo-controlled study performed in 5168 postmenopausal patients with primary breast cancer of positive or unknown receptor status, patients who had remained disease-free after completion of standard adjuvant treatment with tamoxifen (4.5 to 6 years) were randomly assigned to either Femara (n = 2582) or placebo (n = 2586).
The final analysis conducted at the time of unblinding showed that, with regard to the primary endpoint of disease-free survival after median treatment duration of 2.5 years (25% of patients were followed for up to 38 months), Femara reduced the risk of recurrence by 42% compared with placebo (total events 92 [3.6%] for Femara vs. 155 [6%] for placebo; hazard ratio 0.58; p = 0.00003; CI 95%: 0.45, 0.76). Sensitivity analysis confirmed the robustness of the data. On the basis of similar results from the interim analysis, the independent Data Monitoring Committee recommended unblinding the study. The statistically significant benefit in disease-free survival in favour of Femara was irrespective of nodal status (node negative: hazard ratio 0.48; p = 0.00239; CI 95%: 0.30, 0.78; node positive: hazard ratio 0.61; p = 0.00168; CI 95%: 0.44, 0.83), receptor status (positive: hazard ratio 0.57; p = 0.00003; CI 95%: 0.44, 0.75) or prior adjuvant chemotherapy (without: hazard ratio 0.58; p = 0.00330; CI 95%: 0.40, 0.84; with: hazard ratio 0.59; p = 0.00322; CI 95%: 0.41, 0.84).
With regard to the secondary endpoint, overall survival, a total of 113 deaths were reported (51 [2%] Femara, 62 [2.4%] placebo). Overall, the difference between the two groups was not significant (hazard ratio 0.82; p = 0.292; CI 95%: 0.56, 1.19). In the higher risk group of patients with node positive disease, Femara significantly reduced the risk of mortality by approximately 40% (hazard ratio 0.61; p = 0.035; CI 95%: 0.38, 0.97). There was no significant difference in node negative patients (hazard ratio 1.36; p = 0.385; CI 95%: 0.68, 2.71).
There was no difference in safety and efficacy between patients aged < 65 years and patients aged ≥65 years.
The following adverse effects were reported significantly more often with Femara than with placebo, irrespective of causality: hot flushes (49.7% vs. 43.3%), arthralgia/arthritis (27.7% vs. 22.2%) and myalgia (9.5% vs. 6.7%). The incidence of osteoporosis was higher with Femara than with placebo (6.9% vs. 5.5%). The incidence of clinical fractures was slightly higher with Femara (5.9% vs. 5.5%).
Preliminary results (median duration of follow-up: 18 months) from the bone mineral density substudy show that patients receiving Femara had a mean decrease of 3% in hip bone mineral density, compared with 0.4% in the placebo group (p = 0.048). Spinal bone density decreased by 4.6% with Femara vs. 2% with placebo. This difference is not significant. Newly diagnosed osteoporosis was observed in 5.7% of Femara and 4.5% of placebo patients (p = 0.07). Some patients were treated with calcium and bisphosphonates.
Preliminary results (median duration of follow-up: 29 months) from the lipid substudies show no significant difference between the Femara and placebo groups. The incidence of cardiovascular ischaemic complications was comparable between the groups (6.8% vs. 6.5%).
In the Quality of Life analysis (SF-36), there was no clinically relevant difference between Femara and placebo in the scores for physical health, pain and vitality.

First-line treatment of advanced breast cancer

In a controlled trial 2.5 mg Femara was compared with tamoxifen as first-line therapy in 907 postmenopausal women with locally advanced or metastatic breast cancer. Analysis showed that Femara was superior to tamoxifen in the following endpoints, with time to progression as the primary endpoint: Mean time to progression: 9.4 vs. 6.0 months (hazard ratio 0.70, p = 0.0001); overall objective response rate (CR + PR): 32% vs. 21% (odds ratio 1.71, p = 0.001); time to treatment failure: 9.1 vs. 5.7 months (p = 0.0001).
Femara was also superior to tamoxifen as regards objective response rate and time to progression in the subgroups of patients with receptor-positive tumour status or unknown receptor status.
The efficacy of Femara was also superior to that of tamoxifen as regards response rate and time to progression in the subgroup of patients previously treated with antioestrogens.
In patients ≥70 years of age, time to progression was significantly longer with Femara than with tamoxifen – 12.2 vs. 5.8 months (hazard ratio 0.72, p = 0.0001) – and the chance of an objective response with Femara remained significantly higher (odds ratio 1.68, p = 0.0009).
There was also a significant advantage as regards survival (42 vs. 30 months).

Second-line treatment of advanced breast cancer

Two controlled clinical studies were performed to compare two dosage strengths of Femara (0.5 and 2.5 mg) with megestrol acetate in one study and aminoglutethimide in the other, in postmenopausal women with advanced breast cancer previously treated with antioestrogens.
Statistically significant differences were observed in favour of 2.5 mg Femara, compared with megestrol acetate, as regards response rate (24% vs. 16%, p = 0.04) and time to treatment failure (p = 0.04). Time to progression was not significantly different between 2.5 mg Femara and megestrol acetate (p = 0.07). Overall survival was not significantly different between the two treatment arms (p = 0.2).
In the second study, the response rate was not significantly different between 2.5 mg Femara and aminoglutethimide (p = 0.06). 2.5 mg Femara was statistically superior to aminoglutethimide as regards time to progression (p = 0.008), time to treatment failure (p = 0.003) and overall survival (p = 0.002).

Pharmacokinetics

Absorption

Letrozole is rapidly and completely absorbed from the gastrointestinal tract. Mean absolute bioavailability is 99.9%. Concomitant food intake slightly decreases the rate of absorption but has no effect on the extent of absorption (AUC). Letrozole can therefore be taken before, with or after meals.

Distribution

Letrozole is about 60% bound to plasma proteins, mainly albumin (55%). The concentration of letrozole in erythrocytes is about 80% of that in plasma. After administration of 2.5mg ^{14}C-labelled letrozole, approximately 82% of the radioactivity in plasma was unchanged compound. Systemic exposure to metabolites is thus low. Letrozole is rapidly and extensively distributed to tissues. The apparent distribution volume at steady-state is about 1.87 ± 0.47 litres/kg.

Metabolism and Elimination

The major elimination pathway of letrozole, accounting for approximately 95% of total plasma clearance, is metabolic clearance to a pharmacologically inactive carbinol metabolite (Cl_m = 2.1 litres/hour), but this is relatively slow when compared with hepatic blood flow (about 90 litres/hour). CYP3A4 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 two weeks of administration of 2.5 mg ^{14}C-labelled letrozole to healthy postmenopausal volunteers, 88.2 ± 7.6% of the radioactivity was recovered in the urine and 3.8 ± 0.9% in the faeces. At least 75% of the radioactivity recovered in the urine after up to 216 hours (84 ± 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 half-life in plasma is about 75–110 hours. 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, and 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 on 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.

Pharmacokinetics in special patient populations

Elderly patients: Age had no effect on the pharmacokinetics of letrozole.
Renal failure: In a study involving volunteers with varying degrees of kidney function (24 hour creatinine clearance 9–116 ml/minute), no effect on the pharmacokinetics of letrozole was found after single doses of 2.5 mg. In addition, impaired renal function (calculated creatinine clearance 20–50 ml/minute) was not found to have any effect on concentrations of letrozole in patients with advanced breast cancer.
Liver impairment: In a study involving subjects with varying degrees of liver function, the mean AUC values in those with moderate hepatic impairment (Child-Pugh score B) were about 37% higher than in normal subjects, but still within the range seen in subjects without impaired hepatic function. In a study comparing the pharmacokinetics of letrozole after a single dose in 8 patients with liver cirrhosis and severe hepatic impairment (Child-Pugh score C) with the pharmacokinetics in 8 healthy volunteers, AUC and $t_{1/2}$ increased by 95% and 187%, respectively, in the first study population. Higher letrozole levels can thus be expected in breast-cancer patients with severe hepatic impairment than in those without impaired hepatic function. However, as no increase in toxicity was observed in patients receiving daily doses of 5 or 10mg, no dose adjustment is indicated in patients with severe hepatic impairment. Nevertheless, such patients should be closely monitored.

Preclinical data

Neither *in vitro* nor *in vivo* investigations of mutagenic potential revealed any evidence of genotoxicity.
In a conventional carcinogenesis study, doses of 0.6 to 60 mg/kg/day (about 1 to 100 times the daily maximum human dose on a mg/m² basis) were administered by gavage in mice for up to 2 years. This study revealed a dose-related increase in the incidence of benign ovarian stromal tumours. The incidence of combined hepatocellular adenoma and carcinoma showed a significant trend in female mice when the high-dose group was excluded due to low survival. In a separate study, plasma $AUC_{0\text{-}12\ hour}$ levels in mice given a dose of 0.6 mg/kg/day were equivalent to 0.4 times the $AUC_{0\text{-}24\ hour}$ level in breast-cancer patients given the recommended dose.
In a 104 week rat carcinogenicity study, no treatment-related tumours were found. In female rats, a reduced incidence of benign and malignant mammary tumours was determined at all doses of letrozole.
Oral administration of letrozole to pregnant rats resulted in a slight increase in the incidence of fetal malformations in the treated animals. However, it was not possible to determine whether this was an indirect consequence of the pharmacological characteristics (inhibition of oestrogen biosynthesis) or a direct effect of letrozole per se.
Preclinical observations were limited to those associated with the acknowledged pharmacological effect. These were thus the only safety concerns regarding use in humans that arose from the animal studies. Femara is therefore contraindicated during pregnancy and lactation (see **Contraindications**).

Other information

Shelf-life

Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage

Protect from moisture and do not store above 30°C. Keep all medicines out of the reach of children.

Pack sizes

Country specific pack sizes

Manufacturer

See folding box.

Information last revised

July 2007

Date of approval

09 October 2007

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament

- A medicament 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 medicament.
- 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.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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