NOVARTIS

APPROVAL WITH CONDITIONS OF
PrFEMARA* 2.5 MG TABLETS FOR ADJUVANT TREATMENT OF POSTMENOPAUSAL WOMEN WITH HORMONE RECEPTOR POSITIVE EARLY BREAST CANCER

DEAR HEALTH CARE PROFESSIONAL LETTER

September 18, 2006

Dear Health Professional(s):

Novartis Canada Inc. is pleased to announce that Health Canada has granted a Notice of Compliance under the Notice of Compliance with Conditions **(NOC/c)** policy to FEMARA* (letrozole) 2.5 mg tablets for use in the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer. The intended duration of therapy is 5 years, although current data is limited to a median follow-up of 26 months.
Health Canada has issued a marketing authorization with conditions under the Notice of Compliance with Conditions policy for FEMARA* (letrozole) 2.5 mg tablets based on the promising nature of the clinical efficacy and safety of FEMARA as adjuvant treatment for early breast cancer. This authorization is conditional upon further confirmation of clinical benefit.

This NOC/c is based on first planned results of the BIG 1-98 study, a multicenter, double-blind study, randomized with over 8000 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

Patients have been followed for a median of 26 months, 76% of the patients for more than 2 years, and 15% (1197 patients) for 5 years or longer.

The primary endpoint of the trial was disease-free survival (DFS) which was assessed as the time from randomization to the earliest event of loco-regional or distant recurrence (metastases) of the primary disease, development of invasive contralateral breast cancer, appearance of a second non-breast primary tumor or death from any cause. In the overall population, FEMARA reduced the risk of recurrence by

19% compared with tamoxifen (hazard ratio 0.81; *P*=0.003). The 5-year DFS rates were 84.0% for FEMARA and 81.4% for tamoxifen (absolute difference 2.6%). In the overall population, FEMARA also significantly reduced the risk of recurrence compared with tamoxifen whether prior adjuvant chemotherapy was given (hazard ratio 0.72 ; *P*=0.018) or not (hazard ratio 0.84 ; *P*=0.044).

However, a pre-planned, not powered, subset analysis revealed that DFS advantage over tamoxifen was demonstrated in those patients with node positive disease (HR 0.71; 95%CI 0.59-0.85, *P*=0.0002) and was not observed in patients with node negative disease (HR 0.98; 95%CI 0.77-1.25, *P*=0.89), with significant treatment by nodal status interaction.

For the secondary endpoint, overall survival, a total of 358 deaths were reported (166 on FEMARA and 192 on tamoxifen). There was no significant difference between treatments in overall survival (hazard ratio 0.86; *P*=0.15).

Distant disease-free survival (distant metastases), a surrogate for overall survival, differed significantly overall. There was a 27% reduction in the risk in the FEMARA group (hazard ratio 0.73; *P*=0.001).

FEMARA reduced the risk of invasive contralateral breast cancer by almost 40% (19 vs. 31 on FEMARA and tamoxifen arms, respectively), but likely due to the low number of events, this result was not statistically significant. Patients receiving FEMARA, compared to tamoxifen, had fewer second malignancies (1.9% vs 2.4%). Particularly the incidence of endometrial cancer was lower with FEMARA compared to tamoxifen (0.1% vs 0.4%).

Indications and Clinical Use

FEMARA (letrozole) is indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.

Approval is based on superior Disease Free Survival (DFS) compared to tamoxifen from the overall study population, at a median follow-up of 26 months. However, DFS advantage of FEMARA over tamoxifen was not observed in the subset of patients with node negative disease.

Patients should be advised about the conditional nature of the marketing authorization for FEMARA in early adjuvant therapy.

Contraindications

- Premenopausal endocrine status, pregnancy, lactation.
- Patients who are hypersensitive to letrozole, other aromatase inhibitors, or to any ingredients in the formulation or component of the container.

Warnings and Precautions

Cardiovascular Disease: In the adjuvant setting, the use of some aromatase inhibitors, including FEMARA, may increase the risk of cardiovascular events compared to tamoxifen. The overall incidence of cardiovascular events in the BIG 1-98 study for FEMARA and tamoxifen arms was 9.7 vs. 10.5%, respectively. However, a higher incidence of events was seen for FEMARA vs. tamoxifen, including cardiac failure (0.9 vs. 0.4%, respectively), myocardial infarction (0.8 vs. 0.4%, respectively), fatal cardiac events (0.6 vs. 0.3%, respectively) and numerically higher fatal stroke (0.15%, 6 cases vs. 0.03%, 1 case, respectively), and a lower incidence was seen for thromboembolic events (1.4% vs 3.0%, respectively). Patients with non-malignant systemic diseases (cardiovascular, renal, hepatic, lung embolism etc.) which would prevent prolonged follow-up were ineligible from enrollment in the BIG 1-98 trial.

Bone Mineral Density: FEMARA reduces circulating estrogen levels. The use of estrogen lowering agents, including FEMARA, may cause a reduction in bone mineral density.

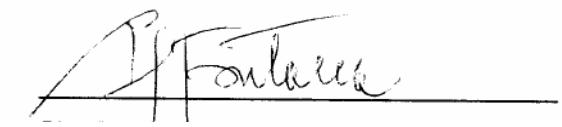
Plasma Lipids: In the adjuvant setting, the use of aromatase inhibitors, including FEMARA, may increase lipid levels.

Adverse Reactions

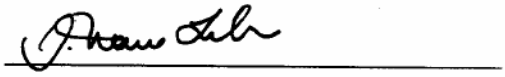
The most frequently reported adverse reactions in the adjuvant setting were hot flushes (letrozole 33.7%, tamoxifen 38.0%), arthralgia/arthritis (letrozole 21.2%, tamoxifen 13.5%), and night sweats (letrozole 14.1%, tamoxifen 16.4%). FEMARA treatment was associated with a significantly higher risk of osteoporosis (2.0 vs. 1.1% with tamoxifen). Bone fractures were significantly higher in the FEMARA arm than the tamoxifen arm (5.7% vs. 4.0%, respectively).

If you have questions concerning FEMARA, please contact our Medical Information Department at 1-800-363-8883.

This document including the FEMARA Prescribing Information and Patient Information can be found on our Website (http:www.novartis.ca).



Pier-Giorgio Fontana PhD
Vice-President, DRA



Jean-Marie Leclerc M.D., F.R.C.P. (C)
Chief Scientific Officer and Senior Vice-President,
Clinical and Regulatory Affairs

Any suspected adverse drug reactions can also be reported to:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Health Product Safety Information Division
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701C
OTTAWA, Ontario, K1A 0K9
Tel: (613) 957-0337 or Fax: (613) 957-0335
Toll free, consumers and health professionals:
Tel: 866 234-2345, Fax: 866 678-6789
e-mail: cadrmp@hc-sc.gc.ca

The ADR Reporting Form can be found in *The Canadian Compendium of Pharmaceuticals and Specialties***, or on the TPD website, along with the ADR Guidelines at:**

http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adverse_e.html
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adr_guideline_e.html

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