HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion

3 January 2007

FEMARA 2.5 mg, film-coated tablet
B/30 tablets (341 474-2)

Applicant: NOVARTIS PHARMA SAS Laboratory

Letrozole

List I

Date of Marketing Authorisation: July 24, 1996 – corrected February 21, 2001 – March 14, 2005 – May 15, 2006

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use in the extension of indication “Adjuvant treatment of hormone receptor-positive early stage breast cancer in menopausal women”.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Letrozole

1.2. Indications

- Adjuvant treatment of hormone receptor-positive early stage breast cancer in menopausal women.

- Prolongation of adjuvant treatment of early-stage breast cancer in menopausal women who have previously received standard adjuvant treatment with tamoxifen for 5 years.

- First-line treatment of hormone dependent advanced breast cancer in menopausal women.

- Treatment of advanced stage breast cancer in menopausal women (natural or artificial menopause) following recurrence or progression of the disease in women previously treated with anti-oestrogens.

The efficacy of letrozole has not been established in breast cancer patients with negative hormone receptors.

1.3. Dosage

The recommended dose of letrozole is 2.5 mg in a single daily dose. No dose adjustment is necessary in elderly patients.
Within the context of adjuvant treatment, it is recommended that treatment be continued for 5 years or until the tumour recurs. Clinical experience available in this indication is 2 years (median duration of treatment is 25 months).

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2005)

L : ANTINEOPLASTICS AND IMMUNOMODULATORS
L02 : THERAPEUTIC ENDOCRINE
L02B : ANTIHORMONES AND RELATED COMPOUNDS
L02BG : ENZYME INHIBITORS
L02BG04 : Letrozole

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines (adjuvant treatment)

Other aromatase inhibitors:

- ARIMIDEX (anastrozole) indicated in the treatment of hormone receptor-positive breast cancer in menopausal women as an adjuvant treatment.

- AROMASIN (exemestane) indicated in the adjuvant treatment of early stage invasive breast cancer expressing oestrogen receptors in menopausal women following initial adjuvant treatment for 2-3 years with tamoxifen.

2.3. Medicines with a similar therapeutic aim

- NOLVADEX (tamoxifen) and generics of this compound
- Cytotoxics indicated for the adjuvant treatment of breast cancer.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The evaluation is based on a phase III, randomised, double-blind clinical study, BIG1-98, which compared letrozole (FEMARA) 2.5 mg/day with tamoxifen (NOLVADEX) 20 mg/day in the adjuvant treatment of breast cancer expressing hormone receptors (oestrogen and/or progesterone receptors) in menopausal women.

This published study[1] started in March 1998 and compared 5 years of FEMARA monotherapy with 5 years of tamoxifen monotherapy. It was amended in April 1999 to propose 4 randomisation groups: FEMARA for 5 years, tamoxifen for 5 years, a sequential treatment of FEMARA for 2 years followed by tamoxifen for 3 years or tamoxifen for 2 years followed by FEMARA for 3 years.

Groups A and B (March 98):
- A: tamoxifen for 5 years
- B: letrozole for 5 years

Groups A, B, C and D (April 99)
- C: tamoxifen for 2 years followed by letrozole for 3 years
- D: letrozole for 2 years followed by tamoxifen for 3 years

Hence, between March 1998 and March 2000, 1835 patients were randomised to 5 years of adjuvant treatment with letrozole or tamoxifen, and between April 1999 and May 2003, 6193 additional women were randomised to one of the 4 treatment groups.

The main analysis specified in the protocol compared the 2 groups of patients initially treated with letrozole or tamoxifen, i.e. the patients assigned to receive monotherapy treatment for the whole 5 years with letrozole or tamoxifen (groups A and B) and the patients in the sequential treatment groups (groups C and D) for whom the events and the follow up were only taken into account from randomisation until a maximum of 30 days after changing treatment as specified by the protocol.
The analysis of monotherapy treatment versus the sequential hormone treatments is not yet available (as the number of events required has not yet been reached).

Primary efficacy endpoint: survival without disease, defined as the time between randomisation and the appearance of the first locoregional event or a distant metastasis of the primitive tumour, the development of invasive breast cancer in the contralateral breast, the appearance of a second primitive tumour that is not a breast cancer, or death from any cause.

Secondary endpoints: overall survival[2], survival without systemic disease (time between randomisation and a systemic recurrence excluding local relapses and cancers of the contralateral breast), location of the first relapse/metastasis, incidence of invasive cancers of the contralateral breast, incidence of secondary non-mammary cancers, cause of death without relapse, tolerance.

[1] Thürlimann B et al, for the Breast International Group (BIG) 1-98 Collaborative Group. A Comparison of Letrozole and Tamoxifen in Postmenopausal Women with Early Breast Cancer. N Engl J Med 2005;353:2747-57.
[2] Defined as the time between randomisation and death from whatever cause

Results:

The median age of patients was 61 years.
Tumour hormone receptors were expressed in all patients.
Adjuvant chemotherapy was instigated following surgery in one quarter of cases.
Median duration of patient follow up was 26 months. Letrozole was administered to 4003 patients and tamoxifen to 4007 patients.

The survival rate without disease (principal endpoint) was 91.2% in the letrozole group versus 89.3% in the tamoxifen group, corresponding to a reduction in relative risk of 19% (RR = 0.81 [0.70 – 0.93]; p = 0.003).
The survival rate without disease estimated at 5 years was 84% in the letrozole group and 81.4% in the tamoxifen group.

No significant difference was observed between the two groups in terms of overall survival.

The reduction in relative risk of survival without metastasis improved by 27% in the letrozole group (RR = 0.73 [0.60; 0.88]; p = 0.001) and that of survival without systemic disease by 17% (RR = 0.83 [0.72; 0.97]; p = 0.02).

No significant difference was observed between the treatments in terms of reduction in risk of invasive breast cancer of the contralateral breast.

An exploratory analysis of survival without disease as a function of lymph node status showed that letrozole was significantly superior to tamoxifen on reduction of risk of relapse in patients with a positive lymph node status (RR = 0.71 [0.59 -0.85]; p = 0.0002) and in patients who had received adjuvant chemotherapy (RR= 0.72 [0.55; 0.95], p = 0.0178). The reduction in risk of relapse in patients with a tumour expressing oestrogen and/or progesterone receptors and treated with letrozole was 20% compared with those treated with tamoxifen (RR = 0.80; [0,69 – 0.92]; p=0.002).

3.2. Adverse events

The most common adverse events observed in the letrozole group were hot flushes, night sweats, arthralgia, weight gain and nausea.

Cardiac insufficiency was reported in 0.9% of cases in the letrozole group and 0.4% of cases in the tamoxifen group.
Osteoporosis was reported in 2.2% of cases in the letrozole group and in 1.2% of cases in the tamoxifen group. There was a 7.1% fracture rate in the letrozole group and a 5.7% fracture rate in the tamoxifen group.
Thromboembolic events occurred at a rate of 1.5% in the letrozole group and 3.2% in the tamoxifen group.
Of those patients who presented with normal total serum cholesterol values at the start of the study, increases in total cholesterol of greater than 1.5 times normal were observed in 5.4% of patients in the letrozole group and 1.1% of patients in the tamoxifen group.

3.3. Conclusion

In a double-blind, randomised study versus tamoxifen in the adjuvant treatment of hormone receptor expressing breast cancer in menopausal women, FEMARA increased the survival rate without disease (principal criterion) by 1.9% (91.2% versus 89.3%, corresponding to a 19% reduction in the relative risk , p=0,003).

No significant difference was observed between the two groups in terms of overall survival. The reduction in relative risk of survival without metastasis improved by 27% in the letrozole group (RR = 0.73 [0.60; 0.88]; p = 0.001) and that of survival without systemic disease by 17% (RR = 0.83 [0.72; 0.97]; p = 0.02).

As far as tolerance is concerned, there was a 0.9% incidence of cardiac insufficiency in the letrozole group and a 0.4% incidence of cardiac insufficiency in the tamoxifen group. There was a 7.1% fracture rate in the letrozole group and a 5.7% fracture rate in the tamoxifen group. Thromboembolic events occurred at a rate of 1.5% in the letrozole group and 3.2% in the tamoxifen group.

It is difficult to make an indirect comparison of the two aromatase inhibitors prescribed at the outset for 5 years in an adjuvant hormone therapy context (BIG 98 study for letrozole and ATAC study for anastrozole) as the median follow up was less in the BIG trial (26 months) than in the ATAC trial (48 months for data evaluated by the Committee in 2004).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Breast cancer is a serious and life-threatening disease;
The efficacy/safety ratio for FEMARA is high;
This medicinal product is intended as curative therapy;
FEMARA is a first-line therapy;
There are alternative treatments in this extension of indication;

Expected public health benefit*:*

Breast cancer is a major public health burden. Among the subpopulation of menopausal patients suffering from early stage breast cancer likely to benefit from FEMARA as an adjuvant treatment, the burden is high.

Improvement of the management of breast cancer is a public health need that lies within the framework of the national cancer strategy.

According to available data, it is expected that FEMARA, for the same reasons as its direct comparator ARIMIDEX, will have only a minor impact on reduction in breast cancer-related morbidity compared with tamoxifen. According to current knowledge, it is not expected to have any impact on reduction in mortality.

As a result, FEMARA is expected to have a public health benefit in this extension to indication. This benefit can be quantified as modest for the same reasons as with ARIMIDEX in this indication.

The actual medical benefit of FEMARA is substantial.

4.2. Improvement in actual benefit

FEMARA, like ARIMIDEX, produces a moderate improvement in actual benefit (level III) in terms of efficacy and tolerance compared with tamoxifen in the indication of the adjuvant treatment of early stage breast cancer in menopausal women.

4.3. Therapeutic use

Following appropriate locoregional treatment combining surgery and radiotherapy, systemic adjuvant treatment must be considered as a function of the Saint Gallen classification [3] :

- Anti-oestrogen hormone therapy in the presence of positive hormone receptors (ER - oestrogen receptor and/or PR positive) in menopausal and pre-menopausal patients, combined in the latter with chemical castration.
- Chemotherapy in all N+ (lymph node involvement) and N- (no lymph node involvement) if the diameter of the tumour is $\geq$ 2 cm or the Scarff Bloom Richardson (SBR) histoprognostic grade is >1 or aged < 35 ans.

In menopausal patients who have to be given chemotherapy and who have hormone positive receptors, a sequential combination of chemotherapy and hormone therapy is recommended and the benefit of these treatments is additive. Tamoxifen has been the standard treatment in this indication for a long time.

[3] Journal of Clinical Oncology, Vol 19, Issue 18 , 2001: 3817-3827

The ATAC[4] trial showed that prescribing an aromatase inhibitor (anastrozole) as an adjuvant in menopausal women presenting with hormone-dependent breast cancer (whether or not they received chemotherapy) increased the survival without relapse compared with tamoxifen alone for 5 years.

In the same way, the use of letrozole[5] and exemestane[6] combined with tamoxifen given in a sequential manner prolongs survival without recurrence compared with 5 years of tamoxifen alone. However, we do not yet know the outcome of the comparison of sequential treatment compared with an aromatase inhibitor initiated at the outset and continued for 5 years.

In conclusion, letrozole (FEMARA) is an alternative to anastrozole (ARIMIDEX) in the adjuvant hormone therapy of menopausal women suffering from non-metastatic breast cancer expressing hormone receptors (ER and/or PR).

4.4. Target population

In 2000, the incidence of breast cancer in France was 42,000[7] cases. The number of cases occurring in menopausal women can be approximately estimated by the number of cases affecting women over 50 years of age: 32,000.
The mean annual increase in the incidence of breast cancer is 2.4%, and therefore the incidence of breast cancer in menopausal women can be estimated as 36,000 in 2005.

Since 5% to 15%[8] of patients were diagnosed from the outset as being at the metastatic stage, 85% to 95% of women have breast cancer where adjuvant treatment is indicated (excluding the advanced stage) following locoregional treatment, i.e. 30,000 to 34,000 menopausal patients in 2005.
Since the mean rate of hormone receptors (HR+) in the population of women suffering from breast cancer was of the order of 80%,[9] [10] the number of menopausal women (HR+) with breast cancer who could benefit from adjuvant treatment is estimated as between 24,000 and 27,000.

The target population of FEMARA in this extension to indication would be of the order of 24,000 to 27,000 cases per year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the new indication and at the posology in the Marketing Authorisation.

4.5.1. Packaging

Appropriate for the prescribing conditions.

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[4] Baum M, et al; ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. The Lancet - Vol. 359, Issue 9324, 22 June 2002, Pages 2131-2139

[5] J Natl Cancer Inst. 2005 Sep 7;97(17):1262-63

[6] N Engl J Med. 2004 Mar 11;350(11):1081-92

[7] « Evolution de l'incidence et de la mortalité par cancer en France de 1978 à 2002 », INVS, octobre 2003 Rise in incidence of cancer mortality in France from 1978 to 2002, INVS, October 2003

[8] Francim/ enquête FNCLCC (survey by National Federation of Centres in the Fight Against Cancer)

[9] Mann GB et al. Reliance on hormone receptor assays of surgical specimens may compromise outcome in patients with breast cancer.J Clin Oncol. 2005 Aug 1; 23(22):5148-54.

[10] Colozza M, Larsimont D, Piccart MJ. Progesterone receptor testing: not the right time to be buried. J Clin Oncol. 2005 Jun 1;23(16):3867-8

4.5.2. Reimbursement rate: 100%