**1.4.3 Package Insert**

## 1. NAME OF THE MEDICINAL PRODUCT

Letrozole Mevon Tablets 2.5 mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: letrozole

Each film-coated tablet contains 2.5 mg letrozole.

Each film-coated tablet contains 77.5 mg lactose.

Full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.
Round tablets with white nucleus and dark yellow coating.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.

Extended adjuvant treatment of early breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy.

First-line treatment in postmenopausal women with advanced hormone-dependent breast cancer.

Treatment of advance breast cancer in women with natural or artificially induced postmenopausal status, who have previously been treated with antioestrogens.

### 4.2 Posology and method of administration

Adults and elderly patients
The recommended dose of Letrozole is 2.5 mg once daily.

In the extended adjuvant setting, the optimal treatment duration with Letrozole is not known. The planned duration of treatment in the study was 5 years. However at the time of the analysis, the median treatment duration was 24 months. 25% of patients were treated for at least 3 years and less than 1% of patients were treated for the planned duration of 5 years. The median duration of follow up was 28 months.
Treatment should be discontinued at tumour relapse. In patients with metastatic disease, treatment with Letrozole should continue until tumour progression is evident. No dose adjustment is required for elderly patients.

In the adjuvant setting, the optimal duration of treatment with letrozole is unknown. The planned duration of treatment in the study is 5 years. However, at the time of analysis, the median duration of treatment was 24 months, median duration of follow-up was 26 months, and 16% of the patients have been treated for 5 years. Treatment should be discontinued at

relapse.

Children
Not applicable.

Patients with hepatic and/or renal impairment
No dosage adjustment is required for patients with hepatic impairment or renal impairment (creatinine clearance ≥10 mL/min.). However, the dose of Letrozole in patients with cirrhosis and severe hepatic dysfunction (Child-Pugh score C) should be reduced by 50% (see PHARMACOKINETICS). The recommended dose of letrozole for such patients is 2.5mg administered every other day. Patients with severe hepatic impairment should be kept under close supervision (see section PHARMACOKINETICS).

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients. Pre-menopausal endocrine status; pregnancy and lactation (see section 5.3).

**4.4 Special warnings and use precautions**

**Bone effects**
During adjuvant treatment with Letrozole, women with osteoporosis or are at risk of osteoporosis should have their bone mineral density formally assessed at the commencement of treatment and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored (see section UNDESIRABLE EFFECTS and PHARMACODYNAMICS).

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

**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 PHARMACOKINETICS).

**Tendon disorders**
The use of third generation aromatase inhibitors, including Letrozole, was found to be associated with tendonitis and tenosynovitis as reported in randomized controlled trials. Tendon rupture was found to be a potential risk. Tendonitis and tenosynovitis were estimated to be of uncommon occurrence, and tendon rupture of rare occurrence. Treating physicians should monitor patients for these adverse drug reactions.

**4.5 Interaction with other medicinal products and other forms of interaction**

Clinical interaction studies with cimetidine and warfarin indicate that the co-administration of Letrozole with these drugs does not result in clinically significant drug interactions.

The review of the clinical tests data bank does not put in evidence other clinically relevant interaction with other commonly prescribed drugs.

There is no clinical experience to date on the use of Letrozole in combination with other anti-cancer agents.

Letrozole inhibits *in vitro* the cytochrome $P_{450}$-isoenzymes 2A6 and moderately 2C19. CYP2A6 and CYP3A4 do not play a major role in the drug metabolism. Nevertheless, caution should be used in the concomitant administration of drugs with bioavailability that is mainly dependent on those isoenzymes and the therapeutic index is narrow.

**4.6 Pregnancy and lactation**

Letrozole is contraindicated in pre-menopausal, pregnant or in lactating women (see section 5.3).

**4.7 Effects on ability to drive and use machines**

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

**4.8 Undesirable effects**

Letrozole was generally well tolerated across all studies as first-line and second-line treatment for advanced breast cancer, as adjuvant treatment of early breast cancer and as extended adjuvant treatment in women who have received prior standard tamoxifen therapy. Approximately one third of the patients treated with Letrozole in the metastatic and neoadjuvant settings, approximately 75% of the patients in the adjuvant setting (both Letrozole and tamoxifen arms, at a median treatment duration of 60 months), and approximately 80% of the patients in the extended adjuvant setting (both Letrozole and placebo arms, at a median treatment duration of 60 months) experienced adverse reactions. Generally, the observed adverse reactions are mainly mild or moderate in nature, and most are associated with 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 Letrozole.

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon ≥1/1000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000), including isolated report.

**Table 1**

**Infections and infestations**
Uncommon – Urinary tract infection

**Neoplasms benign, maglinant and unspecified (including cysts and polyps)**
Uncommon – Tumor pain(6)

**Blood and the lymphatic system disorders**
Uncommon – Leukopenia

**Metabolism and nutrition disorders**
Common – Anorexia, appetite increase, hypercholesterolemia
Uncommon – General oedema

**Psychiatric disorders**

Common – Depression
Uncommon – Anxiety[1]

**Nervous system disorders**
Common – Headache, dizziness
Uncommon – Somnolence, insomnia, memory impairment, dysaesthesia[2] , taste disturbance, cerebrovascular accident

**Eye disorders**
Uncommon – Cataract, eye irritation, blurred vision

**Cardiac disorders**
Uncommon – Palpitations, tachycardia

**Vascular disorders**
Uncommon – Thrombophlebitis[3], hypertension, ischemic cardiac events[7,8]
Rare – Pulmonary embolism, arterial thrombosis, cerebrovascular infarction

**Respiratory, thoracic and mediastinal disorders**
Uncommon – Dysponea

**Gastrointestinal disorders**
Common – Nausea, vomiting, dyspepsia, constipation, diarrhoea
Uncommon – Abdominal pain, stomatitis, dry mouth

**Hepato-biliary disorders**
Uncommon – Increased hepatic enzymes
Very rare – Hepatitis

**Skin and subcutaneous tissue disorders**
Common – Alopecia, increased sweating, rash[4]
Uncommon – Pruritus, dry skin, urticana
Very rare – Angiodedema, anaphylactic reaction, toxic epidermal necrolysis, erythema multiforme

**Musculoskeletal and connective tissue disorders**
Very common – Arthralgia
Common – Myalgia, bone pain, osteoporosis, bone fracture
Uncommon – Arthritis, tendonitis
Rare – Tendon rupture
Not known – Trigger finger

**Renal and urinary disorders**
Uncommon – Increased urinary frequency

**Reproductive system and breast disorders**
Uncommon – Vaginal bleeding, vaginal discharge, vaginal dryness, breast pain

**General diorders and administration site conditions**
Very common – Hot flushes
Common – Fatigue[5], peripheral oedema
Uncommon – Pyrexia, mucosal dryness, thirst

**Investigations**
Common – Weight increase

Uncommon – Weight loss

*Including:
(1) including nervousness, irritability
(2) including paraesthesia, hypoaesthesia
(3) including superficial and deep thrombophlebitis
(4) including erythematous, maculopapular, psoriaform and vesicular rash
(5) including asthenia and malaise
(6) in metastatic/ neoadjuvant setting only
(7) in the adjuvant setting, irrespective of causality, the following adverse events occured in the letrozole and tamoxifen groups respectively: thromboembolic events (2.1% vs 3.6%), angina pectoris (1.1% vs 1.0%), myocardial infarction (1.0% vs 0.5%) and cardiac failure (0.8% vs 0.5%) (see section PHARMACODYNAMICS-Adjuvant treatment).
(8) in the extended adjuvant setting, at a median treatment duration of 60 months for letrozole and 37 months until switch for placebo, the following adverse events were reported for letrozole and placebo respectively: new or worsening angina (1.4% vs 1.0%); angina requiring surgery (0.8% vs 0.6%); myocardial infarction (1.0% vs 0.7%); thromoembolic event (0.9% vs 0.3%); stroke/TIA (1.5% vs 0.8%) (see section PHARMACODYNAMICS-Extended adjuvant treatment)

### 4.9 Overdose

Isolated cases of overdose with Letrozole were reported.
There is no specific treatment for overdose; the treatment must be symptomatic and of support.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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.

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.

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.

## Adjuvant treatment

### Study BIG 1-98

In a multicenter, double-blind study (BIG 1-98) in the adjuvant setting, enrolling over 8000 postmenopausal women with resected, receptor-positive early breast cancer, patients were randomly allocated one of the following treatments:

Option 1:
A. tamoxifen for 5 years
B. Letrozole for 5 years
C. tamoxifen for 2 years followed by Letrozole for 3 years
D. Letrozole for 2 years followed by tamoxifen for 3 years

Option 2:
A. tamoxifen for 5 years
B. Letrozole for 5 years

This study was designed to investigate two primary questions: whether Letrozole 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).

### Efficacy results at a median follow-up of 26 months

Data in Table 2 reflects result of the Primary Core Analysis (PCA) including data from nonswitching arms (arms A and B) together with data truncated 30 days after the switch in the two switching arms (arms C and D). This analysis was conducted at a median treatment duration of 24 months and a median follow-up of 26 months. Letrozole for 5 years was superior to tamoxifen in all endpoints except overall survival and contralateral breast cancer.

Table 2 Disease-free and overall survival (PCA ITT population) at a median follow-up of 26 months

| | Letrozole N=4003 | Tamoxifen N=4007 | Hazard Ratio (95% CI) | P-value[1] |
|---|---|---|---|---|
| Disease-free survival (primary) -events (protocol definition, total) | 351 | 428 | 0.81 (0.70, 0.93) | 0.0030 |
| Time to distant metastases (secondary) | 184 | 249 | 0.73 (0.60, 0.88) | 0.0012 |
| Distant disease free survuval (secondary) | 265 | 318 | 0.82 (0.70, 0.97) | 0.0204 |
| Overall survival (secondary) -number of deaths (total) | 166 | 192 | 0.86 (0.07, 1.06) | 0.1546 |
| Systemic disease-free survival (secondary) | 323 | 383 | 0.83 (0.72, 0.97) | 0.0172 |
| Contralateral breast cancer (invasive) (secondary) | 19 | 31 | 0.61 (0.35, 1.08) | 0.0910 |

CI = confidence interval
(1) Logrank test, stratified by randomization option and use of prior adjuvant chemptherapy

**MAA efficacy results at a median follow-up of 73 months**
The Monotherapy Arms Analysis (MAA) which include data for the monotherapy arms only provides the clinically appropriate long-term update of the efficacy of Letrozole monotherapy compared to tamoxifen monotherapy (Table 3). In 2005, based on the PCA data presented in Table 2 and on recommendations by the independent Data Monitoring Committee, the tamoxifen monotherapy arms were unblinded and patients were allowed to cross over to Letrozole. 26% of patients randomized to tamoxifen elected to cross over to Letrozole – including a very small number of patients who crossed over to other aromatase inhibitors. To explore the impact of this selective crossover, analyses censoring follow-up at the date of the selective crossover (in the tamoxifen arm) are summarized for the MAA (Table 3).

At a median follow-up of 73 months and a median treatment duration of 60 months, the risk of a DFS event was significantly reduced with Letrozole compared with tamoxifen (MAA ITT analysis: HR 0.88; 95% CI 0.78, 0.99; *P*=0.03); confirming the 2005 PCA results. Censored analysis of DFS shows similar benefit (HR 0.85; 95% CI 0.75, 0.96). Similarly, the updated analysis confirmed the superiority of Letrozole in reducing the risk of distant disease free survival events (HR 0.87; 95% CI 0.76, 1.00) and increased time to distant metastases (HR 0.85; 95% CI 0.72, 1.00). Additionally, overall survival trended towards significance in the ITT analysis. Censored analysis of overall survival shows a significantly greater benefit (HR 0.82; 95% CI 0.70, 0.96) in favor of Letrozole.

Table 3 Disease-free and overall survival (MAA ITT poplulation) at a median follow-up of 73 months.

| | Letrozole N=2463 | Tamoxifen N=2459 | Hazard Ration (95% CI) | P-value[1] |
|---|---|---|---|---|
| Disease-free survival (primary) -events (protocol definition, total) | 509 | 565 | 0.88 (0.78, 0.99) | 0.03 |
| Time to distant metastases (secondary) | 257 | 298 | 0.85 (0.72, 1.00) | 0.045 |
| Distant disease-free survival (metastases) (sencondary) | 385 | 432 | 0.87 (0.76, 1.00) | 0.049 |
| Overall survival (secondary) -number of deaths (total) | 303 | 343 | 0.87 (0.75, 1.02) | 0.08 |
| Systemic disease-free survival (secondary) | 465 | 512 | 0.89 (0.79, 1.01) | 0.065 |

| | | | | |
|---|---|---|---|---|
| Contralateral breast cancer (invasive) (sencondary). | 34 | 44 | 0.76 (0.49, 1.19) | 0.2 |
| Censored analysis of DFS | 509 | 543 | 0.85 (0.75, 0.96) | - |
| Censored analysis of Overall survival | 303 | 338 | 0.82 (0.70, 0.96) | - |

CI = confidence interval
(1)Logrank test, stratified by randomization option and use of prior adjuvant chemotheraphy

**Sequential Treatments Analyses**
The Sequential Treatments Analysis (STA) addresses the second primary question of the study, whether switching endocrine agents at about 2 years is more effective than continuing the same agent for a total of 5 years. Only patients in Option 1 participated in the STA. The primary analysis for the STA was from switch (equivalent time-point in monotherapy arms was date of dispensing fifth 6-month treatment pack) + 30 days (STA-S) with a two-sided test applied to each pair-wise comparison at the 2.5% level (to maintain the overall 5% significant level). Additional, exploratory analyses were conducted from randomization (STA-R) with the results for each comparison summarized by hazard ratios and 99% confidence intervals.
At a median follow up of 43 months there were no significant differences in any endpoint from switch in the Sequential Treatments Analysis (STA-S) (e.g. for DFS, [tamoxifen 2 years followed by] Letrozole 3 years versus tamoxifen beyond 2 years, HR 0.85; 97.5% CI 0.67, 1.09 and [Letrozole 2 years followed by] tamoxifen 3 years versus Letrozole beyond 2 years, HR 0.92; 97.5% CI 0.72, 1.17). At a median follow up of 67 months from randomization, there were no significant differences in any endpoint in the Sequential Treatments Analysis from randomization (e.g. for DFS, tamoxifen 2 years followed by Letrozole 3 years versus Letrozole 5 years, HR 1.05; 99% CI 0.84, 1.32; Letrozole 2 years followed by tamoxifen 3 years versus Letrozole 5 years, HR 0.96; 99% CI 0.76, 1.21). There was no evidence that a sequence of Letrozole and tamoxifen was superior to Letrozole alone given for 5 years.

**Safety data at a median treatment duration of 60 months**

In study BIG-98 at a median treatment duration of 60 months, the side effects seen were consistent with the safety profile of the drug. Certain adverse reactions were prospectively specified for analysis, based on the known pharmacologic properties and side effect profiles of the two drugs.

Adverse events were analyzed irrespective of drug relationship. Most adverse events reported (approximately 75% of patients reporting 1 or more AE) were Grade 1 or Grade 2 applying the CTC criteria version 2.0/CTCAE, version 3.0. When considering all grades during study treatment, a higher incidence of events was seen for Letrozole compared to tamoxifen regarding hypercholesterolemia (52% vs. 29%, mostly grade 1 or grade 2), fractures (10.1% vs. 7.1%), myocardial infarctions (1.0% vs. 0.5%), osteoporosis (5.1% vs. 2.7%) and arthralgia (25% vs. 20%).

A higher incidence was seen for tamoxifen compared to Letrozole regarding hot flushes (38% vs. 33%), night sweating (17% vs. 15%), vaginal bleeding (13% vs 5.2%), constipation (2.9% vs 2.0%), thromboembolic events (3.6% vs 2.1%), endometrial hyperplasia/cancer (2.9% vs. 0.3%), and endometrial proliferation disorders (3.5% vs 0.6%).

**Adjuvant Therapy in Early Breast Cancer, Study D2407**

Study D2407 is a phase III, open-label, randomized, multicenter study designed to compare the effects of adjuvant treatment with letrozole to tamoxifen on bone mineral density (BMD), bone markers and fasting serum lipid profiles. A total of 262 postmenopausal women with hormone sensitive resected primary breast cancer were randomly assigned to either letrozole 2.5 mg daily for 5 years or tamoxifen 20 mg daily for 2 years followed by 3 years of letrozole 2.5 mg daily.

The primary objective was to compare the effects on lumbar spine (L2-L4) BMD of letrozole versus tamoxifen, evaluated as percent change from baseline lumbar spine BMD at 2 years.

At 24 months, the lumbar spine (L2-L4) BMD showed a median decrease of 4.1% in the letrozole arm compared to a median increase of 0.3% in the tamoxifen arm (difference = 4.4%). At 2 years, overall the median difference in lumbar spine BMD change between letrozole and tamoxifen was statistically significant in favour of tamoxifen ($P$<0.0001). The current data indicates that no patient with a normal BMD at baseline became osteoporotic at year 2 and only 1 patient with osteopenia at baseline (T score of -1.9) developed osteoporosis during the treatment period (assessment by central review).

The results for total hip BMD were similar to those for lumbar spine BMD. The differences, however, were less pronounced. At 2 years, a significant difference in favour of tamoxifen was observed in the overall BMD safety population and all stratification categories ($P$<0.0001). During the 2 year period, fractures were reported by 20 patients (15%) in the letrozole arm, and 22 patients (17%) in the tamoxifen arm.

In the tamoxifen arm, the median total cholesterol levels decreased by 16% after 6 months compared to baseline; a similar decrease was also observed at subsequent visits up to 24 months. In the letrozole arm, the median total cholesterol levels were relatively stable over time, with no significant increase at a single visit. The differences between the 2 arms were statistically significant in favour of tamoxifen at each time point ($P$<0.0001).

Letrozole reduced the risk of recurrence (including second non-breast primary cancers and death) by 19% compared with tamoxifen (hazard ratio 0.81; 95% CI 0.70, 0.93; $P$=0.003). The 5-year DFS rates were 84.0% for Letrozole and 81.4% for tamoxifen. The improvement in DFS with Letrozole is seen as early as 12 months and is maintained beyond 5 years. Letrozole also significantly reduced the risk of recurrence compared with tamoxifen whether prior adjuvant chemotherapy was given (hazard ratio 0.72; 95% CI 0.55, 0.95) or not (hazard ratio 0.84; 95% CI 0.71, 1.00).

For the secondary endpoint overall survival a total of 358 deaths were reported (166 on Letrozole and 192 on tamoxifen). There was no significant difference between treatments in overall survival (hazard ratio 0.86; 95% CI 0.70, 1.06; $P$=0.15).

**Extended adjuvant treatment**

In a multicenter, double-blind, randomized, placebo-controlled study (CFEM345G MA-17), performed in over 5100 postmenopausal patients with receptor-positive or unknown primary breast cancer patients who had remained disease-free after completion of adjuvant treatment with tamoxifen (4.5 to 6 years) were randomly assigned either Letrozole or placebo.

The primary analysis conducted at a median follow-up of around 28 months (25% of the patients being followed-up for up to 38 months) showed that Letrozole significantly reduced the risk of recurrence by 42 % compared with placebo (hazard ratio 0.58; *P*=0.00003). Sensitivity analyses confirmed the robustness of the data. The statistically significant benefit in DFS in favour of letrozole was observed regardless of nodal status – node negative, hazard ratio 0.48, *P*=0.002; node positive, hazard ratio 0.61, *P*=0.002.

The independent Data and Safety Monitoring Committee recommended that women who were disease-free in the placebo arm be allowed to switch to Letrozole for up to 5 years when the study was unblinded in 2003. In the updated, final analysis conducted in 2008, 1551 women (60% of those eligible to switch) switched from placebo to Letrozole at a median 31 months after completion of adjuvant tamoxifen therapy. Median duration of Letrozole after switch was 40 months.

The updated final analysis conducted at a median follow-up of 62 months confirmed the significant reduction in the risk of breast cancer recurrence with Letrozole compared with placebo, despite 60% of eligible patients in the placebo arm switching to Letrozole after the study was unblinded. In the Letrozole arm, median duration of treatment was 60 months; in the placebo arm, median duration of treatment was 37 months. The protocol-specified 4-year DFS rate was identical in the Letrozole arm for both the 2004 and the 2008 analyses, confirming the stability of the data and robust effectiveness of Letrozole long-term. In the placebo arm, the increase in 4-year DFS rate at the updated analysis clearly reflects the impact of 60% of the patients having switched to Letrozole. This switching also accounts for the apparent dilution in treatment difference.

In the original analysis, for the secondary endpoint overall survival (OS) a total 113 deaths were reported (51 Letrozole, 62 placebo). Overall, there was no significant difference between treatments in OS (hazard ratio 0.82; *P*=0.29). In node positive disease, Letrozole significantly reduced the risk of all-cause mortality by approximately 40% (hazard ratio 0.61; *P*=0.035), whereas no significant difference was seen in patients with node negative disease (hazard ratio 1.36; *P*=0.385), in patient with prior chemotherapy or in patients with no prior chemotherapy. See Tables 4 and 5 that summarize the results:

Table 4 Disease-free and overall survival (Modified ITT population)

| | N=2582 | N=2586 | CI[(2)]<br>P value | N=2582 | N=2586 | CI[(2)]<br>P value |
|---|---|---|---|---|---|---|
| Disease-free survival (protocol definition)[(3)] | | | | | | |
| Events | 92<br>(3.6%) | 155<br>(6.0%) | 0.58<br>(0.45, 0.76)<br>0.00003 | 209<br>(8.1%) | 286<br>(11.1%) | 0.75<br>(0.63, 0.89)<br>0.001 |
| 4-yr DFS rate | 94.4% | 89.8% | | 94.4% | 91.4% | |
| Disease-free survival including deaths from any cause | | | | | | |
| Events | 122<br>(4.7%) | 193<br>(7.5%) | 0.62<br>(0.49, 0.78)<br>0.00003 | 344<br>(13.3%) | 402<br>(15.5%) | 0.89<br>(0.77, 1.03)<br>0.120 |
| 5-yr DFS rate | 90.5% | 80.8% | | 88.8% | 86.7% | |
| Distant metastases | | | | | | |
| Events | 57<br>(2.2%) | 93<br>(3.6%) | 0.61<br>(0.44, 0.84)<br>0.003 | 142<br>(5.5%) | 169<br>(6.5%) | 0.88<br>(0.70,1.10)<br>0.246 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Overall survival | | | | | | |
| Deaths | 51 (2.0%) | 62 (2.4%) | 0.82 (0.56,1.19) 0.291 | 236 (9.1%) | 232 (9.0%) | 1.13 (0.95,1.36) 0.175 |
| Deaths[4] | - | - | - | 236[6] (9.1%) | 170[6] (6.6%) | 0.78 (0.64, 0.96) |
| Contralateral breast cancer | | | | | | |
| Invasive (total) | 15 (0.6%) | 25 (1.0%) | 0.60 (0.31, 1.14) 0.117 | 33 (1.3%) | 51 (2.0%) | 0.64[7] (0.41, 1.00) 0.049 |

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 switching under the ITT principle.
(2) Stratified by receptor status, nodal status and prior adjuvant chemotherapy.
(3) Protocol definition of disease-free survival events; loco-regional recurrance, distant metastasis or contralateral breast cancer.
(4) Exploratory analysis, censoring follow-up times at the date of switch (if it occured) in the placebo arm.
(5) Median follow-up 62 months.
(6) Median follow-up until switch (if it occurred) 37 months.
(7) Odds ratio and 95% CI for the odds ratio.

Table 5 Disease-free and overall survival by receptor status, nodal status and previous chemotherapy (Modified ITT population)

| | 2004 analysis – median follow up 28 months | | 2008 analysis – median follow up 62 months[1] | |
|---|---|---|---|---|
| | HR (95% CI)[2] | P value | HR (95% CI)[2] | P value |
| Disease-free survival (protocol definition) | | | | |
| Receptor status positive | 0.57(0.44, 0.75) | 0.00003 | 0.74(0.62, 0.89) | 0.001 |
| Nodal status | | | | |
| Negative | 0.48(0.30, 0.78) | 0.002 | 0.67(0.49,0.93) | 0.015 |
| Positive | 0.61(0.44, 0.83) | 0.002 | 0.78(0.62, 0.97) | 0.027 |
| Chemotherapy | | | | |
| None | 0.58(0.40,0.84) | 0.003 | 0.71(0.54,0.92) | 0.010 |
| Received | 0.59(0.41,0.84) | 0.003 | 0.79(0.62,1.01) | 0.055 |
| Overall survival | | | | |
| Nodal status | | | | |
| Negative | 1.36(0.68, 2.71) | 0.385 | 1.34(0.99,1.81) | 0.058 |
| Positive | 0.61(0.38,0.97) | 0.035 | 0.96(0.75,1.21) | 0.710 |

HR=Hazards ratio: CI=Confidence interval

(1)Including 60% of eligible patients who switched from placebo to letrozole after the study was unblinded in 2003.

(2) From Cox regression models.

In the updated analysis, as shown in Table 4, there was a significant reduction in the odds of an invasive contralateral breast cancer with Letrozole compared with placebo, despite

60% of the patients in the placebo arm having switched to Letrozole. There was no significant difference in overall survival.

An exploratory analysis censoring follow-up times at the date of switch (if it occurred) showed a significant reduction in the risk of all-cause mortality with Letrozole compared with placebo (Table 4).

There was no difference in efficacy or safety between patients aged <65 versus ≥65 years.

The updated safety profile of Letrozole did not reveal any new adverse event and was entirely consistent with the profile reported in 2004.

The following adverse events irrespective of causality were reported significantly more often with Letrozole than with placebo – hot flushes (Letrozole, 61% versus placebo, 51%), arthralgia/arthritis (41% versus 27%), sweating (35% versus 30%), hypercholesterolemia (24% versus 15%) and myalgia (18% versus 9.4%). The majority of these adverse events were observed during the first year of treatment. In the patients in the placebo arm who switched to Letrozole, a similar pattern of general adverse events was observed. The incidence of osteoporosis during treatment was significantly higher for Letrozole than for placebo (12.2% versus 6.4%). The incidence of clinical fractures during treatment was significantly higher for Letrozole than for placebo (10.4% versus 5.8%). In patients who switched to Letrozole, newly diagnosed osteoporosis during treatement with Letrozole was reported in 5.4% of patients while fractures were reported in 7.7% of patients. Irrespective of treatment, patients ≥65 years experienced more bone fractures and more osteoporosis. Updated results (median follow-up was 61 months) from the bone sub-study demonstrated that, at 2 years, compared to baseline, patients receiving Letrozole had a median decrease of 3.8% in hip Bone Mineral Density (BMD) compared to 2.0% in the placebo group ($P$=0.022). There was no significant difference between treatments in changes in lumbar spine BMD at any time. Updated results (median follow-up was 62 months) from the lipid sub-study showed for any of the lipid measurements no significant difference between the Letrozole and placebo groups at any time. In the updated analysis, the incidence of cardiovascular events (including cerebrovascular and thromboembolic events) during treatment with Letrozole versus placebo until switch was 9.8% vs 7.0%, a statistically significant difference.

Amongst the pre-printed, check-listed terms during study treatment, the most frequently reported events were: stroke/transient ischemic attack (letrozole, 1.5%; placebo until switch, 0.8%); new or worsening angina (letrozole, 1.4%; placebo until switch, 1.0%); myocardial infarction (letrozole, 1.0%; placebo until switch, 0.7%); thromboembolic events (letrozole, 0.9%; placebo until switch, 0.3%). The reported frequency of thromboembolic events as well as of stroke/transient ischemic attack was significantly higher for Letrozole than placebo until switch. The interpretation of safety results should consider that there was an unbalance in the median duration of treatment with letrozole (60 months) compared with placebo (37 months) due to the switch from placebo to Letrozole which occurred in approximately 60% of the patients.

**First-line treatment**
One well-controlled double-blind trial was conducted comparing Letrozole 2.5 mg to tamoxifen as first-line therapy in postmenopausal women with locally advanced or metastatic 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. Specific results are presented in Table 6.

Table 6 Results at a median follow-up of 32 months

| | Letrozole | Tamoxifen | P value |
|---|---|---|---|
| Time to progression (median) | 9.4 months | 6.0 months | <0.0001 |
| Overall objective tumor response (rate) | 32% | 21% | 0.0002 |
| Duration of overall objective tumour response (median) | 25 months | 23 months | 0.0578 |
| Time to treatment failure (median) | 9.1 months | 5.7 months | <0.0001 |
| Clinical benefit (rate) | 50% | 38% | 0.0004 |

Both time to progression and objective response rate were significantly longer/higher for Letrozole than for tamoxifen irrespective of receptor status (Table 7).

Table 7 Receptor status

| | Letrozole | Tamoxifen | P value |
|---|---|---|---|
| Receptor status: | | | |
| ER and/ or PgR+: | | | |
| Time to progression (median) | 9.4 months | 6.0 months | <0.0001 |
| Overall objective tumour response (rate) | 33% | 22% | 0.0019 |
| | | | |
| Unknown/ negative: | | | |
| Time to progression (median) | 9.2 months | 6.0 months | 0.0402 |
| Overall objective tumour response (rate) | 30% | 20% | 0.0309 |

ER: oestrogen receptor
PgR: progesterone receptor

The efficacy by dominant disease site is described in Table 8:

Table 8 Efficacy by dominant disease site

| Dominant disease site | Letrozole n=453 | Tamoxifen n=454 | P value |
|---|---|---|---|
| Soft tissue: | n=113 | n=115 | |
| Time to progression (median) | 12.1 months | 6.4 months | 0.0456 |
| Overall objective tumour response | 50% | 34% | 0.0171 |
| Bone: | n=145 | n=131 | |
| Time to progression (median) | 9.5 months | 6.2 months | 0.0262 |
| Overall obejctive tumour response | 23% | 15% | 0.0891 |
| Viscera: | n=195 | n=208 | |
| Time to progression (median) | 8.3 months | 4.6 months | 0.0005 |
| Overall objective tumour response | 28% | 17% | 0.0095 |
| Liver metastasis: | n=60 | n=55 | |
| Time to progression (median) | 3.8 months | 3.0 months | 0.0232 |
| Overall objective tumour response | 10% | 11% | 0.8735 |
| Rate of overall clinical benefit | 28% | 16% | 0.1292 |
| Overall survival (median) (including crossover) | 19 months | 12 months | 0.0727 |

Note: “Liver metastasis” is a subset of patients with dominant site of disease in viscera.

Study design allowed patients to crossover 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 (Letrozole to tamoxifen) and 13 months (tamoxifen to Letrozole). Letrozole treatment in the first line therapy of advanced breast cancer patients is associated with an early survival advantage over tamoxifen. The median survival was 34

months for Letrozole and 30 months for tamoxifen. A significantly greater number of patients were alive on Letrozole versus tamoxifen throughout the first 24 months of the study (repeated log rank test), see Table 9.

Table 9 Overall survival – Patients alive, died, crossed treatments

| | Letrozole (n=458) | | | Tamoxifen (n=458) | | | Logrank |
|---|---|---|---|---|---|---|---|
| Months | Alive | Deaths | Crossed to tamoxifen | Alive | Deaths | Crossed to letrozole | P value |
| 6 | 426 | 31 | 51 | 406 | 52 | 74 | 0.0167 |
| 12 | 378 | 79 | 129 | 343 | 114 | 145 | 0.0038 |
| 18 | 341 | 115 | 185 | 297 | 159 | 179 | 0.0010 |
| 24 | 286 | 166 | 208 | 263 | 193 | 198 | 0.0246 |
| 30 | 241 | 209 | 225 | 227 | 227 | 217 | 0.0826 |
| 36 | 156 | 243 | 233 | 169 | 251 | 224 | 0.2237 |
| 42 | 70 | 267 | 238 | 85 | 266 | 226 | 0.4820 |
| 48 | 24 | 277 | | 27 | 272 | 228 | 0.6413 |
| 54 | 6 | 277 | | 6 | 276 | | *0.5303 |

*Overall log rank test P-value

The treatment effects analysed by the covariate “prior adjuvant antioestrogen therapy” are detailed in Table 10

Table 10 Results according to prior adjuvant antioestrogen therapy

| | Prior hormone therapy | | | No prior hormone therapy | | |
|---|---|---|---|---|---|---|
| Endpoint | Letrozole n=84 | Tamoxifen n=83 | P value | Letrozole n=369 | Tamoxifen n=371 | P value |
| Time to progression (median) | 8.9 months | 5.9 months | 0.0033 | 9.5 months | 6.0 months | 0.0003 |
| Overall objective tumour response | 26% | 8% | 0.0038 | 33% | 24% | 0.0039 |
| Clinical benefit | 46% | 31% | 0.0464 | 51% | 40% | 0.0026 |
| | n=86 | n=83 | | n=372 | n=375 | |
| Overall survival (median) including crossover | 28 months | 30 months | 0.6558 | 34 months | 30 months | 0.3756 |
| | n=45 | n=43 | | n=174 | n=186 | |
| Survival first-line (Patients who did not crossover) (median) | 33 months | 18 months | 0.001* | 33 months | 19 months | 0.056* |

*The analysis was retrospective, as it was not possible to identify, at baseline, who would cross over and who would not. Overall survival is confounded with crossover. For both of these reasons, no valid inference can be drawn – i.e. the significance level should be viewed with extreme caution.

In patients who did not crossover to the opposite treatment arm, median survival was 35 months with Letrozole (n=219, 95% CI 29 to 43 months) vs. 20 months with tamoxifen (n=229, 95% CI 16 to 26 months).

The total duration of endocrine therapy (time to chemotherapy) was significantly longer for Letrozole (median 16.3 months, 95% CI 15 to 18 months) than for tamoxifen (median 9.3 months, 95% CI 8 to 12 months) (logrank *P*=0.0047).

Worsening of Karnofsky Performance Score (KPS) by 20 points or more occurred in significantly fewer patients on letrozole first-line (19%) than tamoxifen first-line (25%) (odds ratio, *P*=0.0208).

**Second-line treatment**

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

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

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

**Pre-operative treatment**
A double blind trial was conducted in 337 patients randomised to either Letrozole 2.5 mg for 4 months or tamoxifen for 4 months. There were 55% objective responses in the Letrozole-treated patients versus 36% for the tamoxifen-treated patients (*P* <0.001) based on clinical assessment. This finding was consistently confirmed by ultrasound (*P*=0.042) and mammography (*P* <0.001), giving the most conservative assessment of response. This response was reflected in a statistically significantly higher number of patients in the Letrozole group who became suitable for and underwent breast-conserving therapy (45% of patients in the Letrozole group versus 35% of patients in the tamoxifen group, *P*=0.022).

**5.2 Pharmacokinetic properties**

Absorption
Letrozole is rapidly and completely absorbed from the gastrointestinal tract (average absolute bioavailability 99.9%). Food slightly decreases the rate of absorption (median $t_{max}$: 1 hour fasted versus 2 hours fed; and average $C_{max}$: 129 ± 20.3 nmol/litre fasted versus 98.7 ± 18.6 nmol/litre fed) but the level of absorption (AUC) does not change. The minor effect on the absorption rate is not considered to be clinically relevant 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% in relation to that in plasma. After

administration of 2.5 mg $^{14}$C-labelled letrozole, approximately 82% of the radioactivity in plasma was unchanged compound. The systemic exposure to metabolites is therefore low. Letrozole is rapidly and extensively distributed to tissues. Its apparent volume of distribution at steady state is about 1.87 ± 0.47 l/kg.

Metabolism and elimination

The metabolic clearance with a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole ($CL_m$= 2.1 L/h) being, however, 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 two weeks after administration of 2.5 mg $^{14}$C-labelled letrozole to healthy postmenopausal volunteers, 88.2 ± 7.6% of 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.

The apparent terminal elimination half-life in plasma is about 2 days. After daily administration of 2.5 mg steady-state levels are reached within 2 to 6 weeks. Plasma concentrations at steady state are approximately 7 times higher than concentrations measured after a single dose of 2.5 mg, while they are 1.5 to 2 times higher than the steady-state values predicted from the concentrations measured after a single dose, indicating a slight non-linearity in the pharmacokinetics of letrozole upon daily administration of 2.5 mg. Since steady-state is maintained over time, it may be concluded that no continuous accumulation of letrozole occurs.

Age had no effect on the pharmacokinetics of letrozole.

Special populations

In a study involving volunteers with varying degrees of renal function (24-hour creatinine clearance 9 to 116 mL/min), no effect on the pharmacokinetics of letrozole was found after a single dose of 2.5 mg. 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 wellcontrolled 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.

**5.3 Preclinical 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 2000 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. Effects on the liver (increased weight, hepatocellular hypertrophy, fatty

changes) were observed, mainly at high dose levels. Increased incidences of hepatic vacuolation (both sexes, high dose) and necrosis (intermediate and high dose females) were also noted in rats treated for 104 weeks in a carcinogenicity study. They may have been associated with the endocrine effects and hepatin enzyme-inducing properties of Letrozole. However, a direct drug effect cannot be ruled out. 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. In the same study, decreased fertility at all doses 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. In a 104-week mouse carcinogenicity study, dermal and systemic inflammation occurred, particularly at the highest dose of 60 mg/kg, leading to increased mortality at this dose level. Both *in vitro* and *in vivo* investigations on letrozole's mutagenic potential revealed no indication of any genotoxicity. 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. 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 recommendations in sections CONTRAINDICATIONS and PREGNANCY AND LACTATION). In the carcinogenicity studies, no treatment-related tumours were noted in male animals. In female animals,treatment-related changes in genital tract tumours (a reduced incidence of benign and malignant mammary tumours in rats, an increased incidence of benign ovarian stromal tumours in mice) were secondary to the pharmacological effect of the compound. 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.

## 6. PHARMACEUTICAL INFORMATION

### 6.1 List of excipients

**Tablet nucleus**

Lactose Monohydrate
Microcrystalline Cellulose
Maize Starch
Colloidal Anhydrous Silica
Sodium Starch Glycolate
Magnesium Stearate

**Tablet coating**

Polyvinyl Alcohol
Talc
Titanium Dioxide (E171)
Macrogol/PEG 3350
Quinoline yellow Aluminium Lake
Red iron oxide (E172)
Black iron oxide (E172)

(OPADRY II 85F32444 Yellow)

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

36 months

**6.4 Special precautions for storage**

Store at or below 30˚C.

**6.5 Nature and contents of container**

The tablets are packed in ALU + PVDC blister packs with clear PVC + PE + PVDC alveolus.

Blister packs of 10, 30 or 60 tablets (not all presentations are available locally).

**6.6 Special precautions for disposal**

No special requirements.

**7. MARKETING AUTHORIZATION HOLDER**

Novem Pharma Pte Ltd
23 New Industrial Road #03-08, Solstice Business Center Singapore 536209.

**8. MARKETING AUTHORISATION NUMBER(S)**

SIN13916P

**9. DATE OF REVISION OF THE TEXT**
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