SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LETROKS, 2,5 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2,5 mg letrozole (Letrozolum).
Excipients known to: each film-coated tablets contains 40 mg lactose monohydrate

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets
White, round, biconvex film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Advanced breast cancer after relapse or disease progression, in women with natural or artificially induced postmenopausal endocrine status, who have previously been treated with anti-oestrogens.

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

Extended adjuvant treatment of hormone-dependent invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy for 5 years.

Efficacy has not been demonstrated in patients with hormone receptor negative breast cancer.

4.2 Posology and method of administration

Adults:
The recommended dose of medicinal product is 2,5 mg once daily. In the adjuvant and extended adjuvant setting, treatment with medicinal product should continue for 5 years or until tumour relapse occurs, whichever is first. After treatment tamoxifen, treatment with medicinal product should continue for 3 years or until tumour relapse occurs. In patients with metastatic, treatment with letrozole should continue until the evidence of progression of the cancer.

No dose adjustment is required for elderly patients.

Paediatric population
Not applicable.

Renal and hepatic impairment
No dosage adjustment of medicinal product is required for patients with renal insufficiency with creatinine clearance ≥10 ml/min.
Insufficient data are available in cases of renal insufficiency with creatinine clearance lower than 10 ml/min and patients with hepatic impairment (see sections 4.4 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
Contraindication is also the state before menopause, pregnancy and lactation (see section 5.3) and severe hepatic impairment (Child-Pugh C).

4.4 Special warnings and precautions for use

Letrozol has not been investigated in a sufficient number of patients with a creatinine clearance lower than 10 ml/min.
Letrozol was tested on a small number of cancer patients without metastases and with varying degrees of hepatic impairment: mild to moderate and severe hepatic impairment.
In patients with severe hepatic impairment (Child-Pugh C), systemic exposure and terminal half-life were approximately doubled compared to healthy volunteers. Such patients should therefore be kept under close supervision (patrz punkt 4.3).

Medicinal product is a potent oestrogen-lowering agent. Women with a history of osteoporosis and/or fractures, or who are at increased risk of osteoporosis, should have their bone mineral density formally assessed prior to the commencement of adjuvant and extended adjuvant treatment and monitored during and following treatment with letrozole. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored.

As the tablets contain lactose, medicinal product is not recommended for patients with rare hereditary problems of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption

4.5 Interaction with other medicinal products and other forms of interaction

Clinical trials of letrozole interaction with cimetidine and warfarin indicated that no clinically significant interactions when co-administered.

In addition, using the method of review of clinical databases, no clinically significant interactions of letrozole with other commonly used drugs.

There is no clinical experience to date on the use of medicinal product in combination with other anticancer agents.

In vitro, letrozole inhibits the cytochrome P450 isoenzymes 2A6 and, moderately, 2C19, but the clinical relevance is unknown. Caution is therefore indicated when giving letrozole concomitantly with medicinal products whose elimination is mainly dependent on these isoenzymes and whose therapeutic index is narrow.

4.6 Fertility, pregnancy and lactation

Contraindication is also the state before menopause, pregnancy and lactation (see section 4.3)

4.7 Effects on ability to drive and use machines

Medicinal Product has minor influence on the ability to drive and use machines. Since fatigue and dizziness have been observed with the use of {Invented Name} and somnolence has been reported uncommonly, caution is advised when driving or using machines.
4.8 Undesirable effects

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common $\geq 1/10$, common $\geq 1/100$ to $<1/10$, uncommon $\geq 1/1000$ to $<1/100$, rare $\geq 1/10,000$ to $<1/1,000$, very rare $<1/10,000$.

Letrozole was generally well tolerated in all clinical trials, both used in the treatment of first-line and second-line treatment of advanced breast cancer, as well as extended adjuvant therapy in women who have previously received standard treatment with tamoxifen.

Approximately one third of patients treated may experience side effects. The most common hot flashes, nausea and alopecia. Many adverse reactions can be attributed to the pharmacological effects of estrogen deprivation (hot flushes, hair loss and vaginal bleeding).

The following adverse drug reactions were reported:

- **Infections and infestations**
  - Uncommon: Urinary tract infection

- **Neoplasms, benign, malignant and unspecified (including cysts and polyps)**
  - Uncommon: Tumour pain

- **Blood and the lymphatic system disorders**
  - Uncommon: Leukopenia

- **Metabolism and nutrition disorders**
  - Common: Anorexia, appetite increase, Hypercholesterolaemia
  - Uncommon: General edema

- **Psychiatric disorders**
  - Common: Depression
  - Uncommon: Anxiety (including nervousness), irritability

- **Nervous system disorders**
  - Common: Headache, dizziness
  - Uncommon: Somnolence, insomnia, memory impairment, dysaesthesia (including paraesthesia, hypoaesthesia), taste disturbance, cerebrovascular accident

- **Eye disorders**
  - Uncommon: Cataract, eye irritation, blurred vision

- **Cardiac disorders**
  - Uncommon: Palpitations, tachycardia

- **Vascular disorders**
  - Uncommon: Thrombophlebitis (including superficial and deep vein thrombophlebitis)
  - Hypertension, myocardial ischaemia
  - Rare: Pulmonary embolism, arterial thrombosis, cerebrovascular infarction

- **Respiratory, thoracic and mediastinal disorders**
  - Uncommon: Dyspnoea

- **Gastrointestinal disorders**
Common: Nausea, dyspepsia, constipation, abdominal pain, diarrhoea, vomiting
Uncommon: Dry mouth, stomatitis, abdominal pain,

Skin and subcutaneous tissue disorders
Common: Alopecia, rash (including erythematous, maculopapular, psoriaform, and vesicular rash), Increased sweating
Uncommon: Pruritus, urticaria, dry skin

Musculoskeletal and connective tissue disorders
Common: bone pain, Myalgia

Renal and urinary disorders
Uncommon: Increased urinary frequency

Reproductive system and breast disorders
Uncommon: vaginal dryness, breast pain, vaginal bleeding

General disorders and administration site conditions
Very common: hot flushes
Common: Fatigue (including asthenia, malaise), Peripheral oedema
Uncommon: mucosal dryness, thirst, pyrexia

Investigations
Common: Weight increase
Uncommon: Weight loss, increasing the activity of transaminases

Reporting of suspected adverse reactions
After the product is on the market, it is important to report suspected adverse reactions. This allows continuous monitoring of the benefit-risk of use. Persons belonging to healthcare professionals should report any suspected adverse reactions by {current address, telephone, fax number}

4.9 Overdose
Isolated cases of overdose with medicinal product have been reported.
No specific treatment for overdose is known; treatment should be symptomatic and supportive..

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Endocrine therapy. Hormone antagonist and related agents: aromatase inhibitor, ATC code: L02BG04.

The elimination of oestrogen-mediated growth stimulation is a prerequisite for tumour response in cases where the growth of tumour tissue depends on the presence of oestrogens and endocrine therapy is used. In postmenopausal women, oestrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens - primarily androstenedione and testosterone - to oestrone and oestradiol. 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 aromatase cytochrome P450, resulting in a reduction of oestrogen biosynthesis in all tissues where present.
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%, 78% and 78% from baseline, respectively. Maximum suppression is achieved in 48-78 hours.

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 mg to 5 mg suppressed plasma concentration 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 were 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.

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 mg 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 test.

**Extended adjuvant treatment**

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

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

In the secondary endpoint or overall survival, there was 113 deaths (51 letrozole, 62 in the placebo group). There was no significant difference in overall survival between the two groups (hazard ratio 0.82, p = 0.29). In patients with lymph node involvement, letrozole significantly reduced the risk of death by 40% (hazard ratio 0.61, p = 0.035), whereas no significant differences were observed for patients without lymph node metastasis (hazard ratio 1.36, P = 0.385) in patients undergoing chemotherapy frequently and in patients not receiving chemotherapy prior to testing. The results are summarised in Table 1 and 2:

<table>
<thead>
<tr>
<th></th>
<th>Letrozol N=2582</th>
<th>Placebo N=2586</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease-free survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>92 (3,6%)</td>
<td>155 (6,0%)</td>
<td>0,58(0,45;0,76)</td>
<td>p=0,00003</td>
</tr>
<tr>
<td><strong>Distant metastases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>93</td>
<td>0,61(0,44;0,84)</td>
<td>p=0,003</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>51</td>
<td>62</td>
<td>0,82(0,56;1,19)</td>
<td>p=0,292</td>
</tr>
<tr>
<td><strong>Contralateral breast cancer</strong></td>
<td>19</td>
<td>30</td>
<td>0,63(0,36;1,13)</td>
<td>p=0,120</td>
</tr>
<tr>
<td>(secondary criterion)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Including DCIS / LCIS-invasive</td>
<td>15</td>
<td>25</td>
<td>0,60(0,31;1,14)</td>
<td>p=0,117</td>
</tr>
</tbody>
</table>
CI= Confidence Interval, DCIS = ductal carcinoma in situ, LCIS = lobular carcinoma in situ

1 Stratified by receptor status, nodal status and prior adjuvant chemotherapy.
2 Analysis of the layers excluding
3 The odds ratio analysis without taking into account

Table 2 Survival in remission and overall survival with regard to receptor status, nodal status and prior chemotherapy (modified ITT population)

<table>
<thead>
<tr>
<th>Survival in remission</th>
<th>Hazard ratio, 95%CI survival in remission</th>
<th>Value p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Receptor status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- having cancer hormone receptors node status</td>
<td>0,57( 0,44;0,75)</td>
<td>0,00003</td>
</tr>
<tr>
<td><strong>Node status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Without metastases</td>
<td>0,48( 0,30;0,78)</td>
<td>0,00239</td>
</tr>
<tr>
<td>- Metastatic</td>
<td>0,61( 0,44;0,83)</td>
<td>0,00168</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- no</td>
<td>0,58(0,40;0,84)</td>
<td>0,00330</td>
</tr>
<tr>
<td>- conducted</td>
<td>0,59(0,41;0,84)</td>
<td>0,00322</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Node status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Without metastases</td>
<td>1,36(0,68;2,71)</td>
<td>0,385</td>
</tr>
<tr>
<td>- Metastatic</td>
<td>0,61(0,38;0,97)</td>
<td>0,035</td>
</tr>
</tbody>
</table>

CI = Confidence Interval

There were no differences in the efficacy and safety of letrozole between patients aged <65 years and women aged ≥ 65 years.

In letrozole following adverse reactions have been reported with varying causal relationship, which occurred significantly more frequently compared to placebo - hot flushes (49.7% versus 43.3%), pain or arthritis (27.7% in compared to 22.2%) and muscle pain (9.5% versus 6.7%). Most of these side effects were observed in the first year of treatment. The incidence of osteoporosis reported by patients was higher letrozole than in the placebo group (6.9% versus 5.5%). The incidence of fractures was only slightly higher in letrozole -treated patients than in women receiving placebo (5.9% vs. 5.5%). The incidence of fractures in 1000 woman-years letrozole (24.6) is in the range observed for a similar population of healthy women in the postmenopausal period. Preliminary results of the analysis (median of 20 months of observation) based on the study of bone mineral density (BMD) showed that after two years of treatment using letrozole patients there was a 3% decrease of hip BMD relative to baseline, compared to 0.4% values corresponding decrease in the placebo group (p = 0.048). There was no significant difference in the change in BMD for the lumbar spine. Preliminary results of the analysis (median follow-up 29 months) based on the study of lipid profile showed no differences between letrozole and placebo group. In the main study, the incidence of ischemic events was comparable in both treatment arms (6.8% vs. 6.5%).

First-line treatment
One controlled double-blind trial was conducted comparing {Invented Name} (letrozole) 2.5 mg to tamoxifen 20 mg as first-line therapy in postmenopausal women with advanced breast cancer. In 907 women, letrozole was superior to tamoxifen in time to progression (primary endpoint) and in overall objective response, time to treatment failure and clinical benefit. (TTP) - Time to progression, Time to progression (ORR), Treatment failure (TTF), clinical benefit (CBR). The results are summarised in Table 3:
### Table 3.

<table>
<thead>
<tr>
<th></th>
<th>letrozol</th>
<th>tamoxifen</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to progression (TTP)</td>
<td>9.4 months</td>
<td>6.0 months</td>
<td>0.0001</td>
</tr>
<tr>
<td>Time to progression (ORR)</td>
<td>30%</td>
<td>20%</td>
<td>0.0006</td>
</tr>
<tr>
<td>Treatment failure (TTF)</td>
<td>9.1 months</td>
<td>5.7 months</td>
<td>0.0001</td>
</tr>
<tr>
<td>Clinical benefit. (CBR)</td>
<td>49%</td>
<td>38%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Second-line treatment

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

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

In the second study, the response rate was not significantly different between letrozole 2.5 mg and aminoglutethimide (P=0.06). 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).

### 5.2 Pharmacokinetic properties

#### Absorption

Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99.9%). Food slightly decreases the rate of absorption (median tmax 1 hour fasted versus 2 hours fed; and mean Cmax 129 ± 20.3 nmol/litre fasted versus 98.7 ± 18.6 nmol/litre fed) but the extent of absorption (AUC) is not changed. The minor effect on the absorption rate is not considered to be of clinical relevance, and therefore letrozole may be taken without regard to mealtimes.

#### Distribution

Plasma protein binding of letrozole is approximately 60%, mainly to albumin (55%). The concentration of letrozole in erythrocytes is about 80% of that in plasma. After administration of 2.5 mg 14C-labelled letrozole, approximately 82% of the radioactivity in plasma was unchanged compound. 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.

#### Biotransformation

Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole (CLm = 2.1 l/h) but is relatively slow when compared to hepatic blood flow (about 90 l/h). The cytochrome P450 isoenzymes 3A4 and 2A6 were found to be capable of converting letrozole to this metabolite. Formation of minor unidentified metabolites and direct renal and faecal excretion play only a minor role in the overall elimination of letrozole. Within 2 weeks after administration of 2.5 mg 14C-labelled letrozole to healthy postmenopausal volunteers, 88.2 ± 7.6% of the radioactivity was recovered in urine and 3.8 ± 0.9% in faeces. At least 75% of the radioactivity recovered in urine up to 216 hours (84.7 ± 7.8% of the dose) was attributed to the glucuronide of the carbinol metabolite, about 9% to two unidentified metabolites, and 6% to unchanged letrozole.

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 levels are maintained over time, it can be concluded that no continuous accumulation of letrozole occurs.

Age had no effect on the pharmacokinetics of letrozole

**Special populations**

In a study involving 19 volunteers with varying degrees of renal function (24-hour creatinine clearance 9-116 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 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 male subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh C) to those in healthy volunteers (N=8), AUC and t½ increased by 95 and 187%, respectively. Thus, Letroks should be administered with caution to patients with severe hepatic impairment and after consideration of the risk/benefit in the individual patient.

**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 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. The no-adverse-effect level was 0.3 mg/kg in both species.

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

Letrozole was embryotoxic and foetotoxic in pregnant rats and rabbits following oral administration at clinically relevant doses. In rats that had live foetuses, there was an increase in the incidence of foetal malformations including domed head and cervical/centrum vertebral fusion. An increased incidence of foetal malformations was not seen in the rabbit. It is not known whether this was an indirect consequence of the pharmacological properties (inhibition of oestrogen biosynthesis) or a direct drug effect.

Preclinical observations were confined to those associated with the recognised pharmacological action.

The results of these studies support the proposed contraindications contained in section (see sections 4.3 and 4.6).

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

microcrystalline cellulose
lactose monohydrate
maize starch
sodium starch glycolate type C
magnesium stearate

Film coat (Opadry AMB White):
polyvinyl alkohol, titanium dioxide (E 171), talc, soya lecithin, xanthan gum

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in original container.
Keep out of the reach and sight of children.

6.5 Nature and contents of container

HDPE bottle with polypropylene closure and ring warranty, the desiccant, in a cardboard box

6.6 Special precautions for disposal

In order to protect the drug from access by unauthorized persons and children packing cap is provided with a ring warranty and child proof type protection
In order to properly open the package must comply with the following drawings:

① PUSH HARD THE CAP  ② PUSHED CAP TURN ABOUT
HALF THE MARKET

Any unused product or waste material should be disposed of in accordance with local regulations.
7. MARKETING AUTHORISATION HOLDER

Celon Pharma S.A.
ul. Ogrodowa 2A, Kiełpin
05-092 Łomianki
Tel. (22) 751 59 33
Fax. (22) 751 44 58
e-mail: info@celonpharma.com

8. MARKETING AUTHORISATION NUMBER(S)

Marketing authorization number: 10607

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29.04.2004 r.

10. DATE OF REVISION OF THE TEXT