Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Aromasin 25 mg coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance: exemestane
Each coated tablet contains 25 mg exemestane.

Each tablet contains 30.2mg of sucrose and 0.003mg of methyl parahydroxybenzoate (E218).

For a full list of Excipients, see section 6.1

3 PHARMACEUTICAL FORM

Coated tablet

Product imported from Italy:
Round, biconvex, off-white coated tablet marked 7663 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Aromasin is indicated for the adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer, following 2 – 3 years of initial adjuvant tamoxifen therapy.

Aromasin is indicated for the treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-oestrogen therapy. Efficacy has not been demonstrated in patients with oestrogen receptor negative status.

4.2 Posology and method of administration

Adult and elderly patients
The recommended dose of Aromasin is one 25 mg tablet to be taken once daily, preferably after a meal.

In patients with early breast cancer, treatment with Aromasin should continue until completion of five years of combined sequential adjuvant hormonal therapy (tamoxifen followed by Aromasin), or earlier if tumour relapse occurs.

In patients with advanced breast cancer, treatment with Aromasin should continue until tumour progression is evident.

No dose adjustments are required for patients with hepatic or renal insufficiency *(see section 5.2, Pharmacokinetic Properties).*

Children
Not recommended for use in children.

4.3 Contraindications

Aromasin tablets are contraindicated in patients with a known hypersensitivity to the active substance or to any of the excipients, in pre-menopausal women and in pregnant or lactating women.

4.4 Special warnings and precautions for use

Aromasin should not be administered to women with pre-menopausal endocrine status. Therefore, whenever clinically appropriate, the post-menopausal status should be ascertained by assessment of LH, FSH and oestradiol levels.

Aromasin should be used with caution in patients with hepatic or renal impairment.

Aromasin tablets contain sucrose and should not be administered to patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency.

Aromasin tablets contain methyl-p-hydroxybenzoate which may cause allergic reactions (possibly delayed).

Aromasin is a potent oestrogen lowering agent, and a reduction in bone mineral density and an increased fracture rate has been observed following administration (*see section 5.1, Pharmacodynamic properties).* During adjuvant treatment with Aromasin,women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry at the commencement of treatment. Although adequate data to show the effects of therapy in the treatment of the bone mineral density loss caused by Aromasin are not available, treatment for osteoporosis should be initiated in at risk patients. Patients treated with Aromasin should be carefully monitored.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro evidence showed that the drug is metabolised through cytochrome P450 (CYP) 3A4 and aldoketoreductases *(see section 5.2, Pharmacokinetic Properties)* and does not inhibit any of the major CYP isoenzymes. In a clinical pharmacokinetic study, the specific inhibition of CYP 3A4 by ketoconazole showed no significant effects on the pharmacokinetics of exemestane.

In an interaction study with rifampicin, a potent CYP450 inducer, at a dose of 600mg daily and a single dose of exemestane 25mg, the AUC of exemestane was reduced by 54% and Cmax by 41%. Since the clinical relevance of this interaction has not been evaluated, the co-administration of drugs, such as rifampicin, anticonvulsants (e.g. phenytoin and carbamazepine) and herbal preparations containing hypericum perforatum (St John's Wort) known to induce CYP3A4 may reduce the efficacy of Aromasin. Aromasin should be used cautiously with drugs that are metabolised via CYP3A4 and have a narrow therapeutic window. There is no clinical experience of the concomitant use of Aromasin with other anticancer drugs.

Aromasin should not be coadministered with oestrogen-containing medicines as these would negate its pharmacological action.

4.6 Fertility, pregnancy and lactation

Pregnancy

No clinical data on exposed pregnancies are available with Aromasin. Studies on animals have shown reproductive toxicity *(see section 5.3, Preclinical safety data)*. Aromasin is therefore contraindicated in pregnant women.

Lactation

It is not known whether exemestane is excreted into human milk. Aromasin should not be administered to lactating woman.

Women of perimenopausal status or child-bearing potential

The physician needs to discuss the necessity of adequate contraception with women who have the potential to become pregnant including women who are perimenopausal or who have recently become postmenopausal, until their postmenopausal status is fully established *(see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).*

4.7 Effects on ability to drive and use machines

Drowsiness, somnolence, asthenia and dizziness have been reported with the use of the drug. Patients should be advised that, if these events occur, their physical and/or mental abilities required for operating machinery or driving a car may be impaired.

4.8 Undesirable effects

Aromasin was generally well tolerated across all clinical studies conducted with Aromasin at a standard dose of 25 mg/day, and undesirable effects were usually mild to moderate.
The withdrawal rate due to adverse events was 7.4% in patients with early breast cancer receiving adjuvant treatment with Aromasin following initial adjuvant tamoxifen therapy.

The most commonly reported adverse reactions were hot flushes (22%), arthralgia (18%) and fatigue (16%).

The withdrawal rate due to adverse events was 2.8% in the overall patient population with advanced breast cancer. The most commonly reported adverse reactions were hot flushes (14%) and nausea (12%).

Most adverse reactions can be attributed to the normal pharmacological consequences of oestrogen deprivation (e.g. hot flushes).

The reported adverse reactions are listed below by system organ class and by frequency.
Frequencies are defined as: very common (> 10%), common (> 1%, ≤ 10%), uncommon (> 0.1%, ≤ 1%), rare (> 0.01%, ≤ 0.1%).

Metabolism and nutrition disorders:

Common	Anorexia

Psychiatric disorders:

Very common	Insomnia
Common	Depression

Nervous system disorders:

Very common	Headache
Common	Dizziness, carpal tunnel syndrome
Uncommon	Somnolence

Vascular disorders:

Very common	Hot flushes

Gastrointestinal disorders:

Very common	Nausea
Common	Abdominal pain, vomiting, constipation, dyspepsia, diarrhoea

Skin and subcutaneous tissue disorders:

Very common	Increased sweating
Common	Rash, alopecia

Musculoskeletal and bone disorders:

Very common	Joint and musculoskeletal pain (*)
Common	Osteoporosis, fracture

General disorders and administration site conditions:

Very common	Fatigue
Common	Pain, peripheral oedema
Uncommon	Asthenia

(*) Includes: arthralgia, and less frequently pain in limb, osteoarthritis, back pain, arthritis, myalgia and joint stiffness

Blood and lymphatic system disorders
In patients with advanced breast cancer thrombocytopenia and leucopenia have been rarely reported. An occasional decrease in lymphocytes has been observed in approximately 20% of patients receiving Aromasin, particularly in patients with pre-existing lymphopenia; however, mean lymphocyte values in these patients did not change significantly over time and no corresponding increase in viral infections was observed. These effects have not been observed in patients treated in early breast cancer studies.

Hepatobiliary disorders
Elevation of liver function test parameters including enzymes, bilirubin and alkaline phosphatase have been observed.

The table below presents the frequency of pre-specified adverse events and illnesses in the early breast cancer study (IES), irrespective of causality, reported in patients receiving trial therapy and up to 30 days after cessation of trial therapy.

Adverse events and illnesses	**Exemestane (N = 2249)**	**Tamoxifen (N = 2279)**
Hot flushes	491 (21.8%)	457 (20.1%)
Fatigue	367 (16.3%)	344 (15.1%)
Headache	305 (13.6%)	255 (11.2%)
Insomnia	290 (12.9%)	204 (9.0%)
Sweating increased	270 (12.0%)	242 (10.6%)
Gynaecological	235 (10.5%)	340 (14.9%)
Dizziness	224 (10.0%)	200 (8.8%)
Nausea	200 (8.9%)	208 (9.1%)
Osteoporosis	116 (5.2%)	66 (2.9%)
Vaginal haemorrhage	90 (4.0%)	121 (5.3%)
Other primary cancer	84 (3.6%)	125 (5.3%)
Vomiting	50 (2.2%)	54 (2.4%)
Visual disturbance	45 (2.0%)	53 (2.3%)
Thromboembolism	16 (0.7%)	42 (1.8%)
Osteoporotic fracture	14 (0.6%)	12 (0.5%)
Myocardial infarction	13 (0.6%)	4 (0.2%)

In the IES study, the frequency of ischemic cardiac events in the exemestane and tamoxifen treatment arms was 4.5% versus 4.2%, respectively. No significant difference was noted for any individual cardiovascular event including hypertension (9.9% versus 8.4%), myocardial infarction (0.6% versus 0.2%) and cardiac failure (1.1% versus 0.7%).

In the IES study, exemestane was associated with a greater incidence of hypercholesterolemia compared with tamoxifen (3.7% vs. 2.1%).

In a separate double blinded, randomized study of postmenopausal women with early breast cancer at low risk treated with exemestane (N=73) or placebo (N=73) for 24 months , exemestane was associated with an average 7-9% mean reduction in plasma HDL-cholesterol, versus a 1% increase on placebo. There was also a 5-6% reduction in apolipoprotein A1 in the exemestane group versus 0-2% for placebo.

The effect on the other lipid parameters analysed (total cholesterol, LDL cholesterol, triglycerides, apolipoprotein-B and lipoprotein-a) was very similar in the two treatment groups . The clinical significance of these results is unclear.

In the IES study, gastric ulcer was observed at a higher frequency in the exemestane arm compared to tamoxifen (0.7% versus <0.1%). The majority of patients on exemestane with gastric ulcer received concomitant treatment with non-steroidal anti-inflammatory agents and/or had a prior history.

Adverse reactions from post-marketing experience

Hepatobiliary disorders: Hepatitis, cholestatic hepatitis

Because reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

4.9 Overdose

Clinical trials have been conducted with Aromasin given up to 800 mg in a single dose to healthy female volunteers and up to 600 mg daily to postmenopausal women with advanced breast cancer; these dosages were well tolerated. The single dose of Aromasin that could result in life-threatening symptoms is not known. In rats and dogs, lethality was observed after single oral doses equivalent respectively to 2000 and 4000 times the recommended human dose on a mg/m2 basis. There is no specific antidote to overdosage and treatment must be symptomatic. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: steroidal aromatase inhibitor; anti-neoplastic agent

ATC: L02BG06

Exemestane is an irreversible, steroidal aromatase inhibitor, structurally related to the natural substrate androstenedione. In post-menopausal women, oestrogens are produced primarily from the conversion of androgens into oestrogens through the aromatase enzyme in peripheral tissues. Oestrogen deprivation through aromatase inhibition is an effective and selective treatment for hormone dependent breast cancer in postmenopausal women. In postmenopausal women, Aromasin p.o. significantly lowered serum oestrogen concentrations starting from a 5 mg dose, reaching maximal suppression (>90%) with a dose of 10-25 mg. In postmenopausal breast cancer patients treated with the 25 mg daily dose, whole body aromatization was reduced by 98%.

Exemestane does not possess any progestogenic or oestrogenic activity. A slight androgenic activity, probably due to the 17-hydro derivative, has been observed mainly at high doses. In multiple daily doses trials, Aromasin had no detectable effects on adrenal biosynthesis of cortisol or aldosterone, measured before or after ACTH challenge, thus demonstrating its selectivity with regard to the other enzymes involved in the steroidogenic pathway.

Glucocorticoid or mineralocorticoid replacements are therefore not needed. A non dose-dependent slight increase in serum LH and FSH levels has been observed even at low doses: this effect is, however, expected for the pharmacological class and is probably the result of feedback at the pituitary level due to the reduction in oestrogen levels that stimulate the pituitary secretion of gonadotropins also in postmenopausal women.

Adjuvant Treatment of Early Breast Cancer
In a multicentre, randomised, double-blind study, conducted in 4724 postmenopausal patients with oestrogen-receptor-positive or unknown primary breast cancer, patients who had remained disease-free after receiving adjuvant tamoxifen therapy for 2 to 3 years were randomised to receive 3 to 2 years of Aromasin (25 mg/day) or tamoxifen (20 or 30 mg/day) to complete a total of 5 years of hormonal therapy.

After a median duration of therapy of about 30 months and a median follow-up of about 52 months, results showed that sequential treatment with Aromasin after 2 to 3 years of adjuvant tamoxifen therapy was associated with a clinically and statistically significant improvement in disease-free survival (DFS) compared with continuation of tamoxifen therapy. Analysis showed that in the observed study period Aromasin reduced the risk of breast cancer recurrence by 24% compared with tamoxifen (hazard ratio 0.76; p=0.00015). The beneficial effect of exemestane over tamoxifen with respect to DFS was apparent regardless of nodal status or prior chemotherapy.

Aromasin also significantly reduced the risk of contralateral breast cancer (hazard ratio 0.57, p=0.04158).
In the whole study population, a trend for improved overall survival was observed for exemestane (222 deaths) compared to tamoxifen (262 deaths) with a hazard ratio 0.85 (log-rank test: p = 0.07362), representing a 15% reduction in the risk of death in favor of exemestane. A statistically significant 23% reduction in the risk of dying (hazard ratio for overall survival 0.77; Wald chi square test: p = 0.0069) was observed for exemestane compared to tamoxifen when adjusting for the pre−specified prognostic factors (i.e., ER status, nodal status, prior chemotherapy, use of HRT and use of bisphosphonates).

Main efficacy results in all patients (intention to treat population) and oestrogen receptor positive patients are summarised in the table below:

Endpoint Population	**Exemestane Events /N (%)**	**Tamoxifen Events /N (%)**	**Hazard Ratio (95% CI)**	**p-value***
Disease-free survival a				
All patients	354 /2352 (15.1%)	**453** /2372 (19.1%)	0.76 (0.67-0.88)	0.00015
ER+ patients	289 /2023 (14.3%)	**370** /2021 (18.3%)	0.75 (0.65-0.88)	0.00030
Contralateral breast cancer				
All patients	20 /2352 (0.9%)	**35** /2372 (1.5%)	0.57 (0.33-0.99)	0.04158
ER+ patients	18 /2023 (0.9%)	**33** /2021 (1.6%)	0.54 (0.30-0.95)	0.03048
Breast cancer free survival b				
All patients	289 /2352 (12.3%)	**373** /2372 (15.7%)	0.76 (0.65-0.89)	0.00041
ER+ patients	232 /2023 (11.5%)	**305** /2021 (15.1%)	0.73 (0.62-0.87)	0.00038
Distant recurrence free survival c				
All patients	248 /2352 (10.5%)	**297** /2372 (12.5%)	0.83 (0.70-0.98)	0.02621
ER+ patients	194 /2023 (9.6%)	**242** /2021 (12.0%)	0.78 (0.65-0.95)	0.01123
Overall survival d				
All patients	222 /2352 (9.4%)	**262** /2372 (11.0%)	0.85 (0.71-1.02)	0.07362
ER+ patients	178 /2023 (8.8%)	**211** /2021 (10.4%)	0.84 (0.68-1.02)	0.07569

* Log-rank test; ER+ patients = oestrogen receptor positive patients;

[a] Disease-free survival is defined as the first occurrence of local or distant recurrence, contralateral breast cancer, or death from any cause;

[b] Breast cancer free survival is defined as the first occurrence of local or distant recurrence, contralateral breast cancer or breast cancer death;

[c] Distant recurrence free survival is defined as the first occurrence of distant recurrence or breast cancer death;

[d] Overall survival is defined as occurrence of death from any cause.

In the additional analysis for the subset of patients with oestrogen receptor positive or unknown status, the unadjusted overall survival hazard ratio was 0.83 (log-rank test: p = 0.04250), representing a clinically and statistically significant 17% reduction in the risk of dying.

Results from a bone substudy demonstrated that women treated with Aromasin following 2 to 3 years of tamoxifen treatment experienced moderate reduction in bone mineral density. In the overall study, the treatment emergent fracture incidence evaluated during the 30 months treatment period was higher in patients treated with Aromasin compared with tamoxifen (4.5% and 3.3% correspondingly, p=0.038).

Results from an endometrial substudy indicate that after 2 years of treatment there was a median 33% reduction of endometrial thickness in the Aromasin-treated patients compared with no notable variation in the tamoxifen-treated patients. Endometrial thickening, reported at the start of study treatment, was reversed to normal (< 5 mm) for 54% of patients treated with Aromasin.

Treatment of Advanced Breast Cancer

In a randomised peer reviewed controlled clinical trial, Aromasin at the daily dose of 25 mg has demonstrated statistically significant prolongation of survival, Time to Progression (TTP), Time to Treatment Failure (TTF) as compared to a standard hormonal treatment with megestrol acetate in postmenopausal patients with advanced breast cancer that had progressed following, or during, treatment with tamoxifen either as adjuvant therapy or as first-line treatment for advanced disease.

5.2 Pharmacokinetic properties

Absorption:
After oral administration of Aromasin tablets, exemestane is absorbed rapidly. The fraction of the dose absorbed from the gastrointestinal tract is high. The absolute bioavailability in humans is unknown, although it is anticipated to be limited by an extensive first pass effect. A similar effect resulted in an absolute bioavailability in rats and dogs of 5%. After a single dose of 25 mg, maximum plasma levels of 18 ng/ml are reached after 2 hours. Concomitant intake with food increases the bioavailability by 40%.

Distribution:
The volume of distribution of exemestane, not corrected for the oral bioavailability, is ca 20000 l. The kinetics is linear and the terminal elimination half-life is 24 h. Binding to plasma proteins is 90% and is concentration independent. Exemestane and its metabolites do not bind to red blood cells.
Exemestane does not accumulate in an unexpected way after repeated dosing.

Metabolism and excretion:
Exemestane is metabolised by oxidation of the methylene moiety on the 6 position by CYP 3A4 isoenzyme and/or reduction of the 17-keto group by aldoketoreductase followed by conjugation. The clearance of exemestane is ca 500 l/h, not corrected for the oral bioavailability.
The metabolites are inactive or the inhibition of aromatase is less than the parent compound.
The amount excreted unchanged in urine is 1% of the dose. In urine and faeces equal amounts (40%) of ^{14}C-labeled exemestane were eliminated within a week.

Special populations
Age: No significant correlation between the systemic exposure of Aromasin and the age of subjects has been observed.

Renal insufficiency:
In patients with severe renal impairment (CL_{cr} < 30 ml/min) the systemic exposure to exemestane was 2 times higher compared with healthy volunteers.
Given the safety profile of exemestane, no dose adjustment is considered to be necessary.

Hepatic insufficiency:
In patients with moderate or severe hepatic impairment the exposure of exemestane is 2-3 fold higher compared with healthy volunteers. Given the safety profile of exemestane, no dose adjustment is considered to be necessary.

5.3 Preclinical safety data

Toxicological studies:
Findings in the repeat dose toxicology studies in rat and dog were generally attributable to the pharmacological activity of exemestane, such as effects on reproductive and accessory organs. Other toxicological effects (on liver, kidney or central nervous system) were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Mutagenicity:
Exemestane was not genotoxic in bacteria (Ames test), in V79 Chinese hamster cells, in rat hepatocytes or in the mouse micronucleus assay. Although exemestane was clastogenic in lymphocytes *in vitro*, it was not clastogenic in two *in vivo* studies.

Reproductive toxicology*:*
Exemestane was embryotoxic in rats and rabbits at systemic exposure levels similar to those obtained in humans at 25 mg/day. There was no evidence of teratogenicity.

Carcinogenicity:
In a two-year carcinogenicity study in female rats, no treatment-related tumors were observed. In male rats the study was terminated on week 92, because of early death by chronic nephropathy. In a two-year carcinogenicity study in mice, an increase in the incidence of hepatic neoplasms in both genders was observed at the intermediate and high doses (150 and 450 mg/kg/day). This finding is considered to be related to the induction of hepatic microsomal enzymes, an effect observed in mice but not in clinical studies. An increase in the incidence of renal tubular adenomas was also noted in male mice at the high dose (450 mg/kg/day). This change is considered to be species- and gender-specific and occurred at a dose which represents 63-fold greater exposure than occurs at the human therapeutic dose. None of these observed effects is considered to be clinically relevant to the treatment of patients with exemestane.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Silica, colloidal hydrated
Crospovidone
Hypromellose
Magnesium stearate
Mannitol
Microcrystalline cellulose
Sodium starch glycolate (type A)
Polysorbate

Sugar-coating:
Hypromellose
Polyvinyl alcohol
Simeticone
Macrogol
Sucrose;
Magnesium carbonate, light
Titanium dioxide (E171)
Methyl Parahydroxybenzoate (E218)
Cetyl esters wax
Talc
Carnauba wax

Printing ink:
Ethyl alcohol
Shellac
Iron oxides (E172)
Titanium oxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date of this product is the date shown on the container and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

30 tablets in blister packs (Aluminium-PVDC/PVC-PVDC)
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Haemato Pharm GmbH
Lilienthalstr. 5c
D012529 Schonefeld
Germany

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1841/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th November 2012

10 DATE OF REVISION OF THE TEXT

May 2014