Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Exemestane Helm 25mg Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 25 mg exemestane.

Excipients:
Each coated tablet contains 31.63 mg of Sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet
White to off white, round, biconvex, coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Exemestan HELM 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.

Exemestan HELM 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 Exemestan HELM is one 25 mg tablet to be taken once daily, after a meal.

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

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

Hepatic or renal impairment
No dose adjustments are required for patients with hepatic or renal impairment (see section 5.2).

Paediatric population
There is no relevant indication for use of Exemestan Helm in children.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Pre-menopausal women
- Pregnancy
- Lactation

4.4 Special warnings and precautions for use

Exemestan HELM must 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.

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

Exemestan HELM 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). During adjuvant treatment with Exemestan HELM, 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 Exemestan HELM are not available, treatment for osteoporosis should be initiated in at risk patients. Patients treated with Exemestan HELM should be carefully monitored.

Exemestan HELM tablets contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Exemestan HELM tablets contain mannitol which may have a mild laxative effect.

Athletes must be aware that this medicine may cause a positive reaction to ‘anti-doping’ tests.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro evidence showed that the medicinal product is metabolised through cytochrome P450 (CYP) 3A4 and aldoketoreductases (see section 5.2) and does not inhibit any of the major CYP isoenzymes. In a clinical pharmacokinetic study, the specific inhibition of CYP3A4 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 600 mg daily and a single dose of exemestane 25 mg, the AUC of exemestane was reduced by 54% and C_{max} 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 Exemestan HELM.

Exemestan HELM should be used cautiously with medicinal products that are metabolised via CYP3A4 and have a narrow therapeutic window. There is no clinical experience of the concomitant use of Exemestan HELM with other anticancer medicinal products.

Exemestan HELM should not be co-administered with oestrogen-containing medicines as these would negate its pharmacological action.

4.6 Fertility, pregnancy and lactation

For exemestane no clinical data on exposed pregnancies are available. Studies in animals have shown reproductive toxicity (see section 5.3). Exemestan HELM is therefore contraindicated in pregnancy (see section 4.3).
It is not known whether exemestane is excreted into human milk. Exemestan HELM must not be administered to lactating woman.

4.7 Effects on ability to drive and use machines

Exemestan HELM has minor or moderate influence on the ability to drive and use machines. Drowsiness, somnolence, asthenia and dizziness have been reported with the use of the medicinal product. 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

Exemestan HELM was generally well tolerated across all clinical studies conducted with exemestane 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 exemestane following initial adjuvant tamoxifen therapy. The most commonly reported adverse reactions were hot flushes (22 %), arthralgia (18 %) and fatique (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 evaluation of adverse reactions is based on the following definition of frequency:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders
Very common: An occasional decrease in lymphocytes has been observed in approximately 20% of the patients receiving exemestane, particulary in patients receiving exemestane 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.
Rare: Thrombocytopenia and leucopenia (in patients with advanced breast cancer).

Nervous system disorders
Very common: Headache
Common: Dizziness, carpal tunnel syndrome
Uncommon: Somnolence

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 connective tissue disorders
Very common: Joint and musculoskeletal pain (includes: arthralgia, and less frequently pain in limbs, osteoarthritis, back pain, arthritis, myalgia and joint stiffness)
Common: Osteoporosis, fracture

Metabolism and nutrition disorders
Common: Anorexia

Vascular disorders
Very common: Hot flushes

General disorders and administration site conditions
Very common: Fatigue
Common: Pain, peripheral oedema
Uncommon: Asthenia

Hepatobiliary disorders
Not known: Elevation of liver function test parameters including enzymes, bilirubin and alkaline phosphatase

Psychiatric disorders
Very common: Insomnia
Common: Depression

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 = 2,249)**	**Tamoxifen (N = 2,279)**
Hot flushes	491 (21.8%)	457 (20.1%)
Fatique	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 ischaemic 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, 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.

4.9 Overdose

No case of overdose has been reported.

Clinical trials have been conducted with exemestane 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 exemestane 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/m^2 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:Hormone antagonist and related agents, enzyme inhibitors, ATC code: L02BG06

Exemestane is an irreversible, steroidal aromatase inhibitor, structurally related to the natural substrate androstenedione. In postmenopausal 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, oral exemestane 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 aromatisation 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, exemestane 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 4,724 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 2 to 3 years of exemestane (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 exemestan 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 exemestane 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.

Exemestane 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 favour 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	Exemstane Events / N (%)	Tamoxifen Events / N (%)	Hazard Ratio (95% CI)	p-value
Disease-free survival [a]				
All patients	**354 / 2,352 (15.1%)**	**453 / 2,372 (19.1%)**	**0.76 (0.67-0.88)**	**0.00015**
ER + patients	**289 / 2,033 (14.3%)**	**370 / 2,021 (18.3%)**	**0.75 (0.65-0.88)**	**0.00030**
Contralateral breast cancer				
All patients	**20 / 2,352 (0.9%)**	**33 / 2,372 (1.5%)**	**0.57 (0.33-0.99)**	**0.04158**
ER + patients	**18 / 2,023 (0.9%)**	**33 / 2,021 (1.6%)**	**0.54 (0.30-0.95)**	**0.03048**
Breast cancer free survival [b]				
All patients	**289 / 2,352 (12.3%)**	**373 / 2,021 (15.7%)**	**0.76 (0.65-0.89)**	**0.00041**
ER + patients	**232 / 2,023 (11.5%)**	**305 / 2,021 (15.1%)**	**0.73 (0.62-0.87)**	**0.00038**
Distant recurrence free survival [c]				
All patients	**248 / 2,352 (10.5%)**	**297 / 2,372 (12.5%)**	**0.83 (0.70-0.98)**	**0.02621**
ER + patients	**194 / 2,023 (9.6%)**	**242 / 2,021 (12.0%)**	**0.78 (0.65-0.95)**	**0.01123**
Overall survival [d]				
All patients	**222 / 2,352 (9.4%)**	**262 / 2,372 (11.0%)**	**0.85 (0.71-1.02)**	**0.07362**
ER + patients	**178 / 2,023 (8.8%)**	**211 / 2,021 (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 exemestane 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 exemestane 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 exemestane-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 exemestane.

Treatment of Advanced Breast Cancer
In a randomised peer reviewed controlled clinical trial, exemestane 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 Exemestan HELM 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 approx. 20,000 l. The kinetic 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 CYP3A4 isoenzyme and/or reduction of the 17-keto group by aldoketoreductase followed by conjugation. The clearance of exemestane is approx. 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 exemestane and the age of subjects has been observed.

Renal insufficiency
In patients with severe renal impairment (Clcr < 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 tumours 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

- Microcrystalline cellulose
- Crospovidone
- Polysorbate 80
- Mannitol (E 421)
- Colloidal anhydrous silica
- Magnesium stearate
- Sucrose
- Spray-dried Acacia
- Purified talc
- Titanium dioxide (E 171)
- Opaglos (Dehydrated ethanol, Shellac, Beeswax White, Carnauba Wax Yellow)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Store in the original container in order to protect from light

6.5 Nature and contents of container

Aluminium-PVDC/PVC-PVDC blister packs

Pack sizes: 10, 15, 30, 90, 105, 100, 20, 120

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

Helm AG
Nordkanalstraße 28
20097 Hamburg
Germany

8 MARKETING AUTHORISATION NUMBER

PA 1466/3/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th February 2011

10 DATE OF REVISION OF THE TEXT

January 2013