SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Exemestane 25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Exemestane

Each film coated tablet contains 25 mg exemestane.

For full list of excipients, see section 6.1**.**

3 PHARMACEUTICAL FORM

Film-coated tablet.
White to off-white, round compound cup film coated tablet, with “25” on one side and plain on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Exemestane 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.

Exemestane 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 Exemestane is one film-coated tablet (25mg) to be taken orally once a day, after a meal.

In patients with early breast cancer, treatment with Exemestane should continue until completion of five years of combined sequential adjuvant hormonal therapy (tamoxifen followed by Exemestane), or earlier if tumour relapse occurs.
In patients with advanced breast cancer, treatment with Exemestane should continue until tumour progression is evident.
No dose adjustments are required for patients with hepatic or renal insufficiency (see section 5.2).

Children and adolescents
Not recommended for use in children and adolescents

4.3 Contraindications

Exemestane is contraindicated in:
- premenopausal women.
- women who are pregnant or breastfeeding
- patients with hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Exemestane 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.

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

Exemestane 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). At the commencement of adjuvant treatment with Exemestane, women with osteoporosis or at risk of osteoporosis should have treatment baseline bone mineral health assessment, based on current clinical guidelines and practice. Patients with advanced disease should have their bone mineral density (BMD) assessed on a case-by-case basis. Although adequate data to show the effects of therapy in the treatment of the bone mineral density loss caused by Exemestane are not available, patients treated with Exemestane should be carefully monitored and treatment for, or prophylaxis of, osteoporosis should be initiated in at risk patients.

Routine assessment of 25 hydroxy vitamin D levels prior to the start of aromatase inhibitor treatment should be considered, due to the high prevalence of severe deficiency in women with early breast cancer (EBC). Women with Vitamin D deficiency should receive supplementation with Vitamin D.

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 5.2) 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 Exemestane.

Exemestane 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 Exemestane with other anticancer drugs.

Exemestane should not be co-administered 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 Exemestane. Studies on animals have shown reproductive toxicity (See section 5.3). The potential risk for humans is unknown. Exemestane is therefore contraindicated in pregnant women.

Lactation
It is not known whether exemestane is excreted into human milk. Exemestane should not be used during breast-feeding.

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 and 4.4).

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

Exemestane 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 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to ≤ 1/100), rare (≥1/10,000 to <1/1000); Not known (cannot be estimated from the available data).

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Very rare (<1/10,000)	Not known (cannot be estimated from the available data)
Metabolism and nutrition disorders		Anorexia				
Psychiatric disorders	Insomnia	Depression				

Nervous system disorders	Headache	Dizziness, carpal tunnel syndrome, paraesthesia	Somnolence			
Vascular disorders	Hot flushes					
Gastrointestinal disorders	Nausea	Abdominal pain, vomiting, constipation, dyspepsia, diarrhoea				
Skin and subcutaneous tissue disorders	Increased sweating	Rash, alopecia, urticaria, pruritis	(†) Acute generalised exanthematous pustulosis			
Immune system disorders			Hypersensitivity			
Musculoskeletal and bone disorders	Joint and musculoskeletal pain (*)	Osteoporosis, fracture				
General disorders and administration site conditions	Fatigue	Pain, peripheral oedema	Asthenia			
Blood and lymphatic system disorders:			Leucopenia (**)	Thrombocytopenia (**)		Lymphocyte count decreased (**)
Hepatobiliary disorders			Hepatitis (†), cholestatic hepatitis (†) hepatic enzyme increased (†), blood bilirubin increased (†), blood alkaline			

			phosphatase increased (†)			

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

(**) 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 Exemestane, 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.
(†) Frequency calculated by rule of 3/X

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme: www.mhra.gov.uk/yellowcard or search for MHRA Yellow card in Google Play or Apple App Store.

4.9 Overdose

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 overdosing 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 antagonists and related agents, enzyme inhibitors**.**

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, Exemestane 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, 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 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 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 Exemestane 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 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 prespecified 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 sub study 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 sub study 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 Exemestane 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 Exemestane 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:
Mannitol (E421)
Copovidone
Crospovidone
Microcrystalline Cellulose
Silica, colloidal anhydrous
Sodium Starch Glycolate (Type A)
Magnesium Stearate(E470b)

Film coating:
Hypromellose (E464)
Macrogol 400
Titanium Dioxide(E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC-PVdC/Aluminium blisters of:
15, 20, 30, 90, 100, 120 and 200 (Blisters of 10 & 15) film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Rudipharm Limited
Unit 6, Salbrook Road Industrial Estate
Salbrook Road
Redhill, Surrey,
RH1 5GJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 49565/0142

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/09/2025

10 DATE OF REVISION OF THE TEXT

25/09/2025