TECHNICAL SHEET

1. NAME OF THE MEDICINAL PRODUCT

Exemestane Normon 25 mg film-coated tablets EFG.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: exemestane.
Each coated tablet contains 25 mg of exemestane.For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablets)
White or almost white, round, biconvex, coated tablets with "E" printed on one side (punch marked).

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Exemestane Normon is indicated for adjuvant treatment of postmenopausal women with early-stage invasive breast cancer with positive estrogen receptors and after 2 to 3 years of initial adjuvant treatment with tamoxifen.

Exemestane Normon is indicated for the treatment of advanced breast cancer in women in a natural or inducedpostmenopausal state, whose disease has progressed after anti-estrogen therapy. Its efficacy has not been demonstrated in patients with negative estrogen receptors.

4.2. Dosage and method of administration

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

In patients with early-stage breast cancer, exemestane treatment should be continued until a total of 5 years of sequential adjuvant hormonal therapy (tamoxifen followed by exemestane) is completed or sooner if the tumor recurs.

In patients with advanced breast cancer, treatment with exemestane Normon should continue until tumor progression is evident.

Patients with hepatic or renal impairment do not require dosage adjustment (see section

5.2).Pediatric population
Its use in children is not recommended.

4.3. Contraindications

Exemestane is contraindicated in:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.In premenopausal women, pregnancy and lactation.

4.4. Special warnings and precautions for use

Exemestane should not be administered to women with a premenopausal endocrine status. Therefore, when clinically appropriate,postmenopausal status should be assessed by determination of LH, FSH and estradiol levels.

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

Exemestane significantly reduces oestrogen levels and a reduction in bone mineral density and an increase in the fracture rate have been observed after administration (see section 5.1). Therefore, in women with or at risk of osteoporosis and receiving
adjuvant treatment with exemestane, bone densitometry should be performed at the start of treatment. Treatment for osteoporosisshould be initiated in patients at risk although specific conclusive data on the effects of treatment on bone mineral density loss
caused by exemestane are lacking. Patients receiving exemestane should be closely monitored.

Use in athletes
This medicine contains exemestane which may cause a positive result in doping control tests.

Warnings on excipients
This medicine contains less than 23 mg sodium (1 mmol) per tablet, that is to say essentially 'sodium-free'.

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

In vitro results have shown that the drug is metabolised via cytochrome P450 (CYP) 3A4 and aldoketorreductases (see section 5.2) and that it does not inhibit any of the major CYP isoenzymes. In a clinical pharmacokinetic study, specific inhibition of CYP 3A4 by ketoconazole did not show significant effects on the pharmacokinetics of exemestane.

In an interaction study using a daily dose of 600 mg rifampin, a potent CYP3A4 inducer, and a single dose of 25 mg exemestane,exemestane AUC was decreased by 54% and Cmax by 41%. Since the clinical relevance of this interaction has not been evaluated, coadministration of exemestane with drugs that are known CYP3A4 inducers such as rifampin, antiepileptics (e.g., phenytoin and carbamazepine), and herbal preparations containing Hypericum perforatum (St. John's wort) may reduce the efficacy of exemestane.

Exemestane should be used with caution with drugs that are metabolized via CYP3A4 and with a narrow therapeutic index. Thereis no clinical experience of concomitant use of exemestane with other antineoplastic drugs.

Exemestane should not be administered together with medicines containing estrogens since

these may cancel out itspharmacological action.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no clinical data available in pregnant women exposed to exemestane. Animal studies have shown reproductive toxicity(see section 5.3). Therefore, exemestane is contraindicated in pregnant women.

Lactation

It is not known whether exemestane is excreted in human milk. Exemestane should not be administered to nursing women.

Women in perimenopausal state or with the possibility of conceiving

The physician should advise the physician of the need for adequate contraception in women who have the potential tobecome pregnant, including women who are perimenopausal or who are have recently reached postmenopause, until the postmenopausal state is fully established (seesections 4.3 and 4.4).

4.7. Effects on ability to drive and use machines

Lethargy, drowsiness, asthenia and dizziness have been reported with the use of this drug. Patients should beadvised that if these effects occur, their physical and/or mental abilities required for driving or operating machinery may be impaired.

4.8. Adverse reactions

In general, exemestane was well tolerated in all clinical studies conducted at a usual dose of 25 mg/day, and sideeffects were typically mild to moderate.

The discontinuation rate due to adverse reactions was 7.4% in patients with early breast cancer receiving adjuvantexemestane after initial adjuvant tamoxifen treatment. The most frequently reported adverse reactions were hot flushes (22%), arthralgia (18%) and fatigue (16%).

The discontinuation rate due to adverse reactions was 2.8% in all patients with advanced breast cancer. The mostfrequently reported adverse reactions were hot flushes (14%) and nausea (12%).

Most adverse reactions can be attributed to the usual pharmacological consequences of estrogen deprivation (e.g.hot flashes).

The reported adverse reactions are listed below by system organ class and frequency.
Frequencies are defined as:

ÿ Very common (ÿ1/10)
ÿ Common (ÿ1/100 to <1/10)
ÿ Uncommon (ÿ1/1,000 to <1/100)ÿ Rare (ÿ1/10,000 to

<1/1,000)

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 flashes

Gastrointestinal disorders:
Very common: Nausea
Common: Abdominal pain, vomiting, constipation, dyspepsia, diarrhea

Skin and subcutaneous tissue disorders: *Very common:* Increased sweating *Common:* Rash, alopecia

Musculoskeletal and connective tissue disorders: *Very common:* Joint and musculoskeletal pain (*) *Common:* Osteoporosis, fractures

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

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

Blood and lymphatic system disorders
In patients with advanced breast cancer, thrombocytopenia and leukopenia have been reported rarely. Occasional decreases in lymphocyte counts have been observed in approximately 20% of patients treated with exemestane, especially in patients with pre-existing lymphopenia; however, in these patients mean

lymphocyte counts did not change significantlyover time and no corresponding increase in viral infections was observed. These effects have not been observed in patients treated in early-stage breast cancer studies.

Hepatobiliary disorders

An elevation of liver function test parameters, including enzymes, bilirubin and alkaline phosphatase, has been observed.

The table below presents the frequencies of the adverse events and illnesses mentioned above from the Early Breast Cancer(IES) Study, regardless of cause, and reported in patients who received treatment during the clinical trial and up to 30 days after completion of treatment.

Adverse effects and diseases	**Exemestane (N = 2249)**	**Tamoxifen (N = 2279)**
Hot flashes	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%)
Increased sweating	270 (12.0%)	242 (10.6%)
Gynecological	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 bleeding	90 (4.0%)	121 (5.3%)
Other primary cancer	84 (3.6%)	125 (5.3%)
Vomiting	50 (2.2%)	54 (2.4%)
Visual disturbances	45 (2.0%)	53 (2.3%)
Thromboembolism	16 (0.7%)	42 (1.8%)
Osteoporotic fractures	14 (0.6%)	12 (0.5%)

Myocardial infarction	13 (0.6%)	4 (0.2%)

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

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

In a separate, randomized, double-blind study in postmenopausal women with low-risk early-stage breast cancer treated with exemestane (N=73) or placebo (N=73) for 24 months, exemestane was associated with a mean reduction in plasma HDL cholesterol of 7-9%, versus a 1% increase with 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 analyzed (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 ulceration occurred at a slightly higher frequency in the exemestane arm compared with the tamoxifen arm (0.7% versus <0.1%). The majority of patients on exemestane who developed gastric ulceration were receiving concomitant NSAIDs and/or had a previous history of gastric ulceration.

Adverse reactions from post-marketing experience

Hepatobiliary disorders: Hepatitis, cholestatic hepatitis.

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

Reporting suspected adverse reactions
It is important to report suspected adverse reactions to the medicinal product after its authorisation. This allows for continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are encouraged to report any suspected adverse reactions via the Spanish Pharmacovigilance System for Medicinal Products for Human Use: www.notificaRAM.es

4.9. Overdose

Clinical trials have been conducted with exemestane given in single doses of up to 800 mg to healthy female volunteers and up to 600 mg/day to postmenopausal women with advanced breast cancer; these

doses were well tolerated. The single dose of exemestane that would cause life-threatening symptoms is not known. In rats and dogs the single lethal oral dose was equivalent to 2000 and 4000 times, respectively, the recommended human dose (on a mg/m2 basis). There is no specific antidote for overdose; treatment should be symptomatic. Provide general supportive care, including frequent monitoring of vital signs and close surveillance of the patient.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: steroidal aromatase inhibitor; antineoplastic agent, ATC code: L02BG06

Exemestane is an irreversible steroidal aromatase inhibitor structurally related to the natural substrate androstenedione. In postmenopausal women the principal source of estrogen is obtained through the conversion of androgens to estrogens by the aromatase enzyme in peripheral tissues. Estrogen deprivation through aromatase inhibition provides an effective and selective treatment of hormone-dependent breast cancer in postmenopausal women. In postmenopausal women oral exemestane significantly reduced serum estrogen concentrations starting at a dose of 5 mg, with maximal suppression (>90%) being achieved at a dose of 10 - 25 mg. In postmenopausal breast cancer patients treated with a daily dose of 25 mg, whole-body aromatization was reduced by 98%.

Exemestane has no progestogenic or estrogenic activity. The slight androgenic activity, probably due to the 17-hydro derivative, has been observed mainly at high doses. In clinical trials with multiple daily doses, exemestane had no detectable effects on adrenal biosynthesis of cortisol or aldosterone measured before or after ACTH stimulation, demonstrating its selectivity with respect to other enzymes involved in the steroidogenic pathway.

Therefore, no replacement therapy with glucocorticoids or mineralocorticoids is required. Even with low doses, a slight non-dose-dependent increase in serum levels of LH and FSH has been observed; this effect is, however, predictable due to the pharmacological class and is probably the result of feedback at the pituitary level due to the reduction in estrogen levels that stimulate pituitary secretion of gonadotropins also in postmenopausal women.

Adjuvant treatment of early-stage breast cancer

In a multicenter, randomized, double-blind study in 4724 postmenopausal patients with estrogen receptor-positive or unknown breast cancer who had remained disease-free after receiving adjuvant tamoxifen for 2 to 3 years, were randomized to receive 2 to 3 years of exemestane (25 mg/day) or tamoxifen (20 or 30 mg/day) for a total of 5 years of hormonal therapy.

After a median treatment duration of about 30 months and a median follow-up of about 52 months, the results showed that sequential treatment with exemestane after 2 to 3 years of adjuvant tamoxifen treatment was associated with a clinically and statistically significant improvement in disease - free survival (DFS) compared with continued tamoxifen treatment. The analysis showed that over the 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 clear regardless

of nodal status or whether or not prior chemotherapy had been received.

Exemestane also produced a significant reduction in the risk of contralateral breast cancer (hazard ratio *0.57 :* p=0.04158).

In the total study population, a trend towards improved overall survival was observed with exemestane (222 deaths) compared with tamoxifen (262 deaths) with a hazard ratio *of* 0.85 (log-rank test: p=0.07362), which represents a 15% reduction in the risk of death in favour of exemestane. A statistically significant reduction in the risk of death of 23% (hazard ratio *for* overall survival of 0.77; Wald Chi-square test: p=0.0069) was observed with exemestane compared with tamoxifen when previously adjusted for prognostic factors.

specified (e.g., estrogen receptor status, nodal status, prior chemotherapy, use of hormone replacement therapy, anduse of bisphosphonates).

The main efficacy results in the total patients (intention-to-treat population) and in patients with estrogen receptorpositivity are summarized in the table below.

Variable	**Exemestane**	**Tamoxifen**	**Risk rate**	**p-value***
Population	**Events/N (%)**	**Events/N (%)**	**(95% CI)**	
Disease-free survival				
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%)[b]	0.54 (0.30-0.95)	0.03048
Breast cancer free survival				
All the 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	All **248** /2352 (10.5%)	**297** / 2372 patients[c]	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	All **222** / 2352 (9.4%)	**262** /2372 (11.0%)	0.85 (0.71-1.02)	*d* patients

0.07362

ER+ patients	**178** /2023 (8.8%)	**211** /2021 (10.4%) 0.84 (0.68-1.02)	0.07569

*Long-rank test; ER+ patients = patients with positive estrogen receptor.

to Disease-free survival is defined as the first case of local or distant recurrence, contralateral breast cancer, or death from any cause.

b Breast cancer-free survival is defined as the first case of local or distant recurrence, contralateral breast cancer, or death from breast cancer.

c Distant recurrence-free survival is defined as the first case of distant recurrence or death from breast cancer.

d Overall survival is defined as the incidence of death from any cause.

In the additional analysis for the subgroup of patients with positive or unknown estrogen receptor, the unadjustedoverall survival *hazard ratio* was 0.83 (log-rank test: p= 0.04250), which represents a clinically and statistically significant 17% reduction in the risk of death.

~~Results from a bone substudy showed that women treated with exemestane after 2 or 3 years of tamoxifen~~ treatment had a moderate reduction in bone mineral density. In all patients included in the study, treatment showed that the incidence of fractures assessed during the 30-month treatment period was higher in patients treated with exemestanecompared to those treated with tamoxifen (4.5% and 3.3% respectively, p=0.038).

Results from the endometrium substudy indicate that after 2 years of treatment, there was a median reduction in endometrial thickness of 33% in patients treated with exemestane compared with patients treated with tamoxifen, inwhom there was no notable variation. Endometrial thickening, observed at the beginning of the study treatment, returned to normal levels (< 5 mm) in 54% of patients treated with exemestane.

Treatment of advanced breast cancer

In a peer-reviewed, randomized, controlled clinical trial, a daily dose of 25 mg exemestane was shown to produce astatistically significant increase in survival, time

to progression (PT) and time to treatment failure (TTF), compared with standard hormonal therapy with megestrol acetate in postmenopausal patients with advanced breast cancer that has progressed after or during treatment with tamoxifen, either as adjuvant therapy or as first-line treatment for advanced disease.

5.2. Pharmacokinetic properties

Absorption:
Following oral administration of exemestane tablets, exemestane is rapidly absorbed. The fraction of the dose absorbed from the gastrointestinal tract is high. Absolute bioavailability in humans is not known, but isanticipated to be limited by a large first-pass effect. A similar effect resulted in an absolute bioavailability of 5% in rats and dogs. Following a single dose of 25 mg, peak plasma levels of 18 ng/ml are reached within 2 hours. Concomitant administration with food increases bioavailability by 40%.

Distribution:
The volume of distribution of exemestane, not corrected for oral bioavailability, is approximately 20,000 L.The kinetics are linear and the terminal elimination half-life is 24 h. Plasma protein binding is 90% and is independent of concentration. Exemestane and its metabolites do not bind to red blood cells.

Exemestane does not accumulate unexpectedly after repeated doses.

Metabolism and excretion:
Exemestane is metabolized by oxidation of the methylene group at position 6 by the isoenzyme CYP 3A4 and/or reduction of the 17-keto group by aldoketoreductase followed by conjugation. The clearance of exemestane is approximately 500 L/h, not corrected for oral bioavailability.
The metabolites are inactive or their ability to inhibit aromatase is less than that of the parent compound.

The amount of unchanged drug excreted in urine is 1% of the dose. The same amount (40%) of 14C-labeled exemestane waseliminated in urine and feces within one week.

Special populations

Age: No significant correlation has been observed between systemic exposure to exemestane and the ageof the subjects.

Kidney failure:
In patients with severe renal impairment (creatinine clearance ÿ 30 ml/min) systemic exposure to exemestane was twice as high compared to healthy volunteers.
Given the safety profile of exemestane, no dose adjustment is considered necessary.

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

5.3. Preclinical safety data

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

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

Reproductive toxicity: Exemestane was embryotoxic in rats and rabbits at systemic exposure levels similar to those in humansat 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 at week 92 due to premature death from chronic kidney disease. In a two-year carcinogenicity study in mice,
an increased incidence of liver neoplasia was observed in both sexes at the intermediate and high doses (150 and 450 mg/kg/day).This finding is thought to be related to the induction of hepatic microsomal enzymes, an effect observed in mice but not in clinical trials. An increased incidence of renal tubular adenoma was also observed in male mice at the high dose (450 mg/kg/day).

This change is considered to be genus- and species-specific and occurred at a dose level representing an exposure of the orderof 63 times that occurring in humans at therapeutic doses. None of these observed effects are considered to be clinically relevantto the treatment of patients with exemestane.

6. PHARMACEUTICAL DATA

6.1. List of excipients

~~Tablet core:~~
Microcrystalline
cellulose Mannitol
Crospovidone
Sodium carboxymethyl starch
(type A) Low substituted
hydroxypropylcellulose
Hydroxypropyl
methylcellulose Macrogol
~~6000~~
Polysorbate 80
colloidal silica
Magnesium
Stearate

Covering:
Hydroxypropyl methylcellulose
Titanium dioxide
(E-171) Talc
Macrogol 6000

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

36 Months.

6.4. Special precautions for storage

It does not require special storage conditions.

6.5. Nature and contents of the container

30 tablets in blisters (Aluminium/PVC-PVDC).

6.6. Special precautions for disposal and other handling None special.

7. MARKETING AUTHORIZATION HOLDER

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Office No 28, 2nd Floor, Rose Plaza
I-8 Markaz, Islamabad.

MANUFACTURED BY

NORMON LABORATORIES, S.A.
Valdecarrizo Roundabout, 6
28760 Tres Cantos-Madrid,
SPAIN

8. MARKETING AUTHORIZATION NUMBER(S)

084588

9. DATE OF FIRST MARKET AUTHORIZATION / RENEWAL OF REGISTRATION

Date of first Registration / Market Authorization: 5th Jun 2017Date of latest renewal: 4th Jun 2027

10. DATE OF TEXT REVISION

Detailed information on this medicine is available on the website of the Spanish Agency forMedicines and Health Products (AEMPS) (http://www.aemps.gob.es/)