SAMENVATTING VAN DE PRODUCTKENMERKEN

1. NAAM VAN HET GENEESMIDDEL

Imarsa 250 mg oplossing voor injectie in een voorgevulde spuit

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe of 5 ml contains 250 mg fulvestrant.

Excipients with known effect (per 5 ml)
Ethanol 96% (alcohol), 500 mg
Benzyl alcohol (E1519), 500 mg
Benzyl benzoate, 750 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe

Clear, colorless to yellow, viscous solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fulvestrant is indicated:

- as monotherapy for the treatment of estrogen receptor positive, locally advanced or metastatic breast cancer in postmenopausal women:
    - not previously treated with endocrine therapy, or
    - with disease relapse on or after adjuvant antiestrogen therapy, or disease progression on antiestrogen therapy.
- in combination with palbociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in women who have received prior endocrine therapy (see section 5.1).

In pre- or perimenopausal women, the combination treatment with palbociclib should be combined with a luteinizing hormone releasing hormone (LHRH) agonist.

4.2 Posology and method of administration

Posology

Adult females (including elderly)
The recommended dose is 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose.

When fulvestrant is used in combination with palbociclib, please also refer to the Summary of Product Characteristics of palbociclib.

Prior to the start of treatment with the combination of fulvestrant plus palbociclib, and throughout its duration, pre/perimenopausal women should be treated with LHRH agonists according to local clinical practice.

Special population

Renal impairment
No dose adjustments are recommended for patients with mild to moderate renal impairment (creatinine clearance ≥ 30 ml/min). Safety and efficacy have not been evaluated in patients with severe renal impairment (creatinine clearance < 30 ml/min), and, therefore, caution is recommended in these patients (see section 4.4).

Hepatic impairment
No dose adjustments are recommended for patients with mild to moderate hepatic impairment. However, as fulvestrant exposure may be increased, fulvestrant should be used with caution in these patients. There are no data in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Paediatric population
The safety and efficacy of fulvestrant in children from birth to 18 years of age have not been established. Currently available data are described in sections 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration
Fulvestrant should be administered as two consecutive 5 ml injections by slow intramuscular injection (1-2 minutes/injection), one in each buttock (gluteal area)

Caution should be taken if injecting fulvestrant at the dorsogluteal site due to the proximity of the underlying sciatic nerve.

For detailed instructions for administration, see section 6.6.

4.3 Contraindications

hypersensitivity to the active substance or to any of the excipients listed in section 6.1
pregnancy and lactation (see section 4.6)
severe hepatic impairment (see sections 4.4 and 5.2).

4.4 Special warnings and precautions for use

Fulvestrant should be used with caution in patients with mild to moderate hepatic impairment (see sections 4.2, 4.3 and 5.2).

Fulvestrant should be used with caution in patients with severe renal impairment (creatinine clearance less than 30 ml/min).

Due to the intramuscular route of administration, fulvestrant should be used with caution if treating patients with bleeding diatheses, thrombocytopenia or those taking anticoagulant treatment.

Thromboembolic events are commonly observed in women with advanced breast cancer and have been observed in clinical trials with fulvestrant (see section 4.8). This should be taken into consideration when prescribing fulvestrant to patients at risk.

Injection site related events including sciatica, neuralgia, neuropathic pain, and peripheral neuropathy have been reported with fulvestrant injection. Caution should be taken while administering fulvestrant at the dorsogluteal injection site due to the proximity of the underlying sciatic nerve (see sections 4.2 and 4.8).

There are no long-term data on the effect of fulvestrant on bone. Due to the mechanism of action of fulvestrant, there is a potential risk of osteoporosis.

The efficacy and safety of fulvestrant (either as monotherapy or in combination with palbociclib) have not been studied in patients with critical visceral disease.

When fulvestrant is combined with palbociclib, please also refer to the Summary of Product Characteristics of palbociclib.

Interference with estradiol antibody assays
Due to the structural similarity of fulvestrant and estradiol, fulvestrant may interfere with antibody based-estradiol assays and may result in falsely increased levels of estradiol.

Ethanol
This medicinal product contains 500 mg of alcohol (ethanol) in each injection which is equivalent to 100 mg/ ml (10% w/v). The amount in each injection of this medicine is equivalent to 13 ml beer or 5 ml wine.

A dose of 500 mg of this medicine (two syringes) administered to an adult women weighing 70 kg would result in exposure to 14.3 mg / kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 2.4 mg /100 ml (see Appendix I of report EMA/CHMP/43486/2018). For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/ 100 ml.

Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects.

Benzyl alcohol
This medicinal product contains benzyl alcohol as an excipient which may cause allergic reactions.

Paediatric population
Fulvestrant is not recommended for use in children and adolescents as safety and efficacy have not been established in this group of patients (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

A clinical interaction study with midazolam (substrate of CYP3A4) demonstrated that fulvestrant does not inhibit CYP3A4. Clinical interaction studies with rifampicin (inducer of CYP3A4) and ketoconazole (inhibitor of CYP3A4) showed no clinically relevant change in fulvestrant clearance.
Dose adjustment is therefore not necessary in patients who are receiving fulvestrant and CYP3A4 inhibitors or inducers concomitantly.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Patients of childbearing potential should use effective contraception during treatment with Imarsa and for 2 years after the last dose.

Pregnancy

Fulvestrant is contraindicated in pregnancy (see section 4.3). Fulvestrant has been shown to cross the placenta after single intramuscular doses in rat and rabbit. Studies in animals have shown reproductive toxicity including an increased incidence of foetal abnormalities and deaths (see section 5.3). If pregnancy occurs while taking fulvestrant, the patient must be informed of the potential hazard to the foetus and potential risk for loss of pregnancy.

Breast-feeding
Breast-feeding must be discontinued during treatment with fulvestrant. Fulvestrant is excreted in milk in lactating rats. It is not known whether fulvestrant is excreted in human milk. Considering the potential for serious adverse reactions due to fulvestrant in breast-fed infants, use during lactation is contraindicated (see section 4.3).

Fertility
The effects of fulvestrant on fertility in humans has not been studied.

4.7 Effects on ability to drive and use machines

Fulvestrant has no or negligible influence on the ability to drive or use machines. However, since asthenia has been reported very commonly with fulvestrant, caution should be observed by those patients who experience this adverse reaction when driving or operating machinery.

4.8 Undesirable effects

Summary of safety profile
Monotherapy
This section provides information based on all adverse reactions from clinical trials, post-marketing studies or spontaneous reports. In the pooled dataset of fulvestrant monotherapy, the most frequently reported adverse reactions are injection site reactions, asthenia, nausea, and increased hepatic enzymes (ALT, AST, ALP).

In Table 1, the following frequency categories for adverse drug reactions (ADRs) were calculated based on the fulvestrant 500 mg treatment group in pooled safety analyses of studies that compared fulvestrant 500 mg with fulvestrant 250 mg [CONFIRM (Study D6997C00002), FINDER 1 (Study D6997C00004), FINDER 2 (Study D6997C00006), and NEWEST (Study D6997C00003) studies], or from FALCON (Study D699BC00001) alone that compared fulvestrant 500 mg with anastrozole 1 mg. Where frequencies differ between the pooled safety analysis and FALCON, the highest frequency is presented. The frequencies in the following table were based on all reported adverse drug reactions, regardless of the investigator assessment of causality. The median duration of fulvestrant 500 mg treatment across the pooled dataset (including the studies mentioned above plus FALCON) was 6.5 months.

Tabulated list of adverse reactions
Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency groupings are defined according to the following convention: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100). Within each frequency grouping adverse reactions are reported in order of decreasing seriousness.

Table 1 Adverse Drug Reactions reported in patients treated with fulvestrant monotherapy

Adverse reactions by system organ class and frequency		
Infections and infestations	Common	Urinary tract infections
Blood and lymphatic system disorders	Common	Reduced platelet count[e]
Immune system disorders	Very common	Hypersensitivity reactions[e]
	Uncommon	Anaphylactic reactions

Metabolism and nutrition disorders	Common	Anorexia[a]
Nervous system disorders	Common	Headache
Vascular disorders	Very common	Hot flushes[e]
	Common	Venous thromboembolism[a]
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting, diarrhoea
Hepatobiliary disorders	Very common	Elevated hepatic enzymes (ALT, AST, ALP)[a]
	Common	Elevated bilirubin[a]
	Uncommon	Hepatic failure[c,f], hepatitis[f], elevated gamma-GT[f]
Skin and subcutaneous tissue disorders	Very common	Rash[e]
	Very common	Joint and musculoskeletal pain[d]
Musculoskeletal and connective tissue disorders	Common	Back pain[a]
Reproductive system and breast disorders	Common	Vaginal haemorrhage[e]
	Uncommon	Vaginal moniliasis[f], leukorrhea[f]
General disorders and administration site conditions	Very common	Asthenia[a], injection site reactions[b]
	Common	Neuropathy peripheral[e], sciatica[e]
	Uncommon	Injection site haemorrhage[f], injection site haematoma[f], neuralgia[c,f]

a. Includes adverse drug reactions for which the exact contribution of fulvestrant cannot be assessed due to the underlying disease.

b. The term injection site reactions does not include the terms injection site haemorrhage and injection site haematoma, sciatica, neuralgia and neuropathy peripheral.

c. The event was not observed in major clinical studies (CONFIRM, FINDER 1, FINDER 2, NEWEST). The frequency has been calculated using the upper limit of the 95% confidence interval for the point estimate. This is calculated as 3/560 (where 560 is the number of patients in the major clinical studies), which equates to a frequency category of 'uncommon'.

d. Includes: arthralgia, and less frequently musculoskeletal pain, myalgia and pain in extremity.

e. Frequency category differs between pooled safety dataset and FALCON.

f. ADR was not observed in FALCON.

Description of selected adverse reactions

The descriptions included below are based on the safety analysis set of 228 patients who received at least one (1) dose of fulvestrant and 232 patients who received at least one (1) dose of anastrozole, respectively in the Phase 3 FALCON study.

Joint and musculoskeletal pain

In the FALCON study, the number of patients who reported an adverse reaction of joint and musculoskeletal pain was 65 (31.2%) and 48 (24.1%) for fulvestrant and anastrozole arms, respectively. Of the 65 patients in the fulvestrant arm, 40% (26/65) of patients reported joint and musculoskeletal pain within the first month of treatment, and 66.2% (43/65) of patients within the first 3 months of treatment. No patients reported events that were CTCAE Grade ≥3 or that required a dose reduction, dose interruption, or discontinued treatment due to these adverse reactions.

Combination therapy with palbociclib

The overall safety profile of fulvestrant when used in combination with palbociclib is based on data from 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer in the randomised PALOMA3 study (see section 5.1). The most common (≥20%) adverse reactions of any grade reported in patients receiving fulvestrant in combination with palbociclib were neutropenia, leukopenia, infections, fatigue, nausea, anaemia, stomatitis, diarrhoea,

thrombocytopenia and vomiting. The most common (≥2%) Grade ≥3 adverse reactions were neutropenia, leukopenia, anaemia, infections, AST increased, thrombocytopenia, and fatigue.

Table 2 reports the adverse reactions from PALOMA3.
Median duration of exposure to fulvestrant was 11.2 months in the fulvestrant + palbociclib arm and 4.8 months in the fulvestrant + placebo arm. Median duration of exposure to palbociclib in the fulvestrant + palbociclib arm was 10.8 months.

Table 2 Adverse reactions based on PALOMA3 Study (N=517)

System Organ Class **Frequency** **Preferred Term**[a]	**Fulvestrant + palbociclib (N=345)**		**Fulvestrant + placebo (N=172)**	
	All Grades n (%)	**Grade ≥3 n (%)**	**All Grades n (%)**	**Grade ≥3 n (%)**
Infections and infestations				
Very common				
System Organ Class **Frequency** **Preferred Term**[a]	**Fulvestrant + palbociclib (N=345)**		**Fulvestrant + placebo (N=172)**	
	All Grades n (%)	**Grade ≥3 n (%)**	**All Grades n (%)**	**Grade ≥3 n (%)**
Very common				
Infections[b]	188 (54.5)	19 (5.5)	60 (34.9)	6 (3.5)
Blood and lymphatic system disorders				
Very common				
Neutropenia[c]	290 (84.1)	240 (69.6)	6 (3.5)	0
Leukopenia[d]	207 (60.0)	132 (38.3)	9 (5.2)	1 (0.6)
Anaemia[e]	109 (31.6)	15 (4.3)	24 (14.0)	4 (2.3)
Thrombocytopenia[f]	88 (25.5)	10 (2.9)	0	0
Uncommon				
Febrile neutropenia	3 (0.9)	3 (0.9)	0	0
Metabolism and nutrition disorders				
Very common				
Decreased appetite	60 (17.4)	4 (1.2)	18 (10.5)	1 (0.6)
Nervous system disorders				
Common				
Dysgeusia	27 (7.8)	0	6 (3.5)	0
Eye disorders				
Common				
Lacrimation increased	25 (7.2)	0	2 (1.2)	0
Vision blurred	24 (7.0)	0	3 (1.7)	0
Dry eye	15 (4.3)	0	3 (1.7)	0
Respiratory, thoracic and mediastinal disorders				
Common				
Epistaxis	25 (7.2)	0	4 (2.3)	0
Gastrointestinal disorders				
Very common				
Nausea	124 (35.9)	2 (0.6)	53 (30.8)	1 (0.6)
Stomatitis[g]	104 (30.1)	3 (0.9)	24 (14.0)	0
Diarrhoea	94 (27.2)	0	35 (20.3)	2 (1.2)
Vomiting	75 (21.7)	2 (0.6)	28 (16.3)	1 (0.6)
Skin and subcutaneous tissue disorders				

Very common				
Alopecia	67 (19.4)	NA	11 (6.4)	NA
Rash[h]	63 (18.3)	3 (0.9)	10 (5.8)	0
Common				
Dry skin	28 (8.1)	0	3 (1.7)	0
General disorders and administration site conditions				
Very common				
Fatigue	152 (44.1)	9 (2.6)	54 (31.4)	2 (1.2)
Pyrexia	47 (13.6)	1 (0.3)	10 (5.8)	0
Common				
Asthenia	27 (7.8)	1 (0.3)	13 (7.6)	2 (1.2)
Investigations				
Very Common				
AST increased	40 (11.6)	11 (3.2)	13 (7.6)	4 (2.3)
Common				
ALT increased	30 (8.7)	7 (2.0)	10 (5.8)	1 (0.6)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; N/n=number of patients; NA=Not applicable

[a] Preferred Terms (PTs) are listed according to MedDRA 17.1.

[b] Infections includes all PTs that are part of the System Organ Class Infections and infestations.

[c] Neutropenia includes the following PTs: Neutropenia, Neutrophil count decreased.

[d] Leukopenia includes the following PTs: Leukopenia, White blood cell count decreased.

[e] Anaemia includes the following PTs: Anaemia, Haemoglobin decreased, Haematocrit decreased.

[f] Thrombocytopenia includes the following PTs: Thrombocytopenia, Platelet count decreased.

[g] Stomatitis includes the following PTs: Aphthous stomatitis, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis.

[h] Rash includes the following PTs: Rash, Rash maculo-papular, Rash pruritic, Rash erythematous, Rash papular, Dermatitis, Dermatitis acneiform, Toxic skin eruption.

Description of selected adverse reactions

Neutropenia

In patients receiving fulvestrant in combination with palbociclib in the PALOMA3 study, neutropenia of any grade was reported in 290 (84.1%) patients, with Grade 3 neutropenia being reported in 200 (58.0%) patients, and Grade 4 neutropenia being reported in 40 (11.6%)patients. In the fulvestrant + placebo arm (n=172), neutropenia of any grade was reported in 6 (3.5%) patients. There were no reports of Grade 3 and 4 neutropenia in the fulvestrant + placebo arm.

In patients receiving fulvestrant in combination with palbociclib, the median time to first episode of any grade neutropenia was 15 days (range: 13-512 days) and the median duration of Grade ≥3 neutropenia was 16 days. Febrile neutropenia has been reported in 3 (0.9%) patients receiving fulvestrant in combination with palbociclib.

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 the national reporting system listed in Appendix V.

4.9 Overdose

There are isolated reports of overdose with fulvestrant in humans. If overdose occurs, symptomatic supportive treatment is recommended. Animal studies suggest that no effects other than those related directly or indirectly to anti-estrogenic activity were evident with higher doses of fulvestrant (see section 5.3).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy, Anti-estrogens, ATC code: L02BA03

Mechanism of action and pharmacodynamic effects

Fulvestrant is a competitive estrogen receptor (ER) antagonist with an affinity comparable to estradiol. Fulvestrant blocks the trophic actions of estrogens without any partial agonist (estrogen-like) activity. The mechanism of action is associated with down-regulation of estrogen receptor protein levels. Clinical trials in postmenopausal women with primary breast cancer have shown that fulvestrant significantly down-regulates ER protein in ER positive tumours compared with placebo. There was also a significant decrease in progesterone receptor expression consistent with a lack of intrinsic estrogen agonist effects. It has also been shown that fulvestrant 500 mg downregulates ER and the proliferation marker Ki67, to a greater degree than fulvestrant 250 mg in breast tumours in postmenopausal neoadjuvant setting.

Clinical efficacy and safety in advanced breast cancer

Monotherapy

A phase3 clinical trial was completed in 736 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. The study included 423 patients whose disease had recurred or progressed during anti-estrogen therapy (AE subgroup) and 313 patients whose disease had recurred or progressed during aromatase inhibitor therapy (AI subgroup). This trial compared the efficacy and safety of fulvestrant 500mg (n=362) with fulvestrant 250mg (n=374). Progression-free survival (PFS) was the primary endpoint; key secondary efficacy endpoints included objective response rate (ORR), clinical benefit rate (CBR) and overall survival (OS). Efficacy results for the CONFIRM study are summarized in Table 3.

Table 3 Summary of results of the primary efficacy endpoint (PFS) and key secondary efficacy endpoints in the CONFIRM study

Variable	**Type of estimate; treatment comparison**	**Fulvestrant 500 mg (N=362)**	**Fulvestrant 250 mg (N=374)**	**Comparison between groups (Fulvestrant 500 mg/Fulvestrant 250 mg)**		
				Hazard ratio	**95% CI**	**p-value**
PFS	**K-M median in months; hazard ratio**					
All Patients		6.5	5.5	0.80	0.68, 0.94	0.006
-AE subgroup (n=423)		8.6	5.8	0.76	0.62, 0.94	0.013
-AI subgroup (n=313)[a]		5.4	4.1	0.85	0.67, 1.08	0.195
OS[b]	**K-M median in months; hazard ratio**					
All Patients		26.4	22.3	0.81	0.69, 0.96	0.016[c]
-AE subgroup (n=423)		30.6	23.9	0.79	0.63, 0.99	0.038[c]
-AI subgroup (n=313)[a]		24.1	20.8	0.86	0.67, 1.11	0.241[c]
Variable	**Type of estimate;**	**Fulvestrant 500 mg**	**Fulvestrant 250 mg**	**Comparison between groups (Fulvestrant 500 mg/Fulvestrant 250 mg)**		

	treatment comparison	(N=362)	(N=374)	Absolute difference in %	95% CI
ORR[d]	**% of patients with OR; absolute difference in %**				
All Patients		13.8	14.6	-0.8	-5.8, 6.3
-AE subgroup (n=296)		18.1	19.1	-1.0	-8.2, 9.3
-AI subgroup (n=205)[a]		7.3	8.3	-1.0	-5.5, 9.8
CBR[e]	**% of patients with CB; absolute difference in %**				
All Patients		45.6	39.6	6.0	-1.1, 13.3
-AE subgroup (n=423)		52.4	45.1	7.3	-2.2, 16.6
-AI subgroup (n=313)[a]		36.2	32.3	3.9	-6.1, 15.2

[a] Fulvestrant is indicated in patients whose disease had recurred or progressed on an anti-estrogen therapy. The results in the AI subgroup are inconclusive.

[b] OS is presented for the final survival analyses at 75% maturity.

[c] Nominal p-value with no adjustments made for multiplicity between the initial overall survival analyses at 50% maturity and the updated survival analyses at 75% maturity.

[d] ORR was assessed in patients who were evaluable for response at baseline (i.e., those with measurable disease at baseline: 240 patients in the fulvestrant 500 mg group and 261 patients in the fulvestrant 250 mg group).

[e] Patients with a best objective response of complete response, partial response or stable disease ≥24 weeks.

PFS:Progression-free survival; ORR:Objective response rate; OR:Objective response; CBR:Clinical benefit rate; CB:Clinical benefit; OS:Overall survival; K-M:Kaplan-Meier; CI:Confidence interval; AI:Aromatase inhibitor; AE:Anti-estrogen.

A Phase 3, randomised, double-blind, double-dummy, multicentre study of fulvestrant 500 mg versus anastrozole 1 mg was conducted in postmenopausal women with ER-positive and/or PgR-positive locally advanced or metastatic breast cancer who had not previously been treated with any hormonal therapy. A total of 462 patients were randomised 1:1 sequentially to receive either fulvestrant 500 mg or anastrozole 1 mg.
Randomisation was stratified by disease setting (locally advanced or metastatic), prior chemotherapy for advanced disease, and measurable disease.

The primary efficacy endpoint of the study was investigator assessed progression-free survival (PFS) evaluated according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumours). Key secondary efficacy endpoints included overall survival (OS) and objective response rate (ORR).

Patients enrolled in this study had a median age of 63 years (range 36-90). The majority of patients (87.0%) had metastatic disease at baseline. Fifty-five percent (55.0%) of patients had visceral metastasis at baseline. A total of 17.1% of patients received a prior chemotherapy regimen for advanced disease; 84.2% of patients had measurable disease.

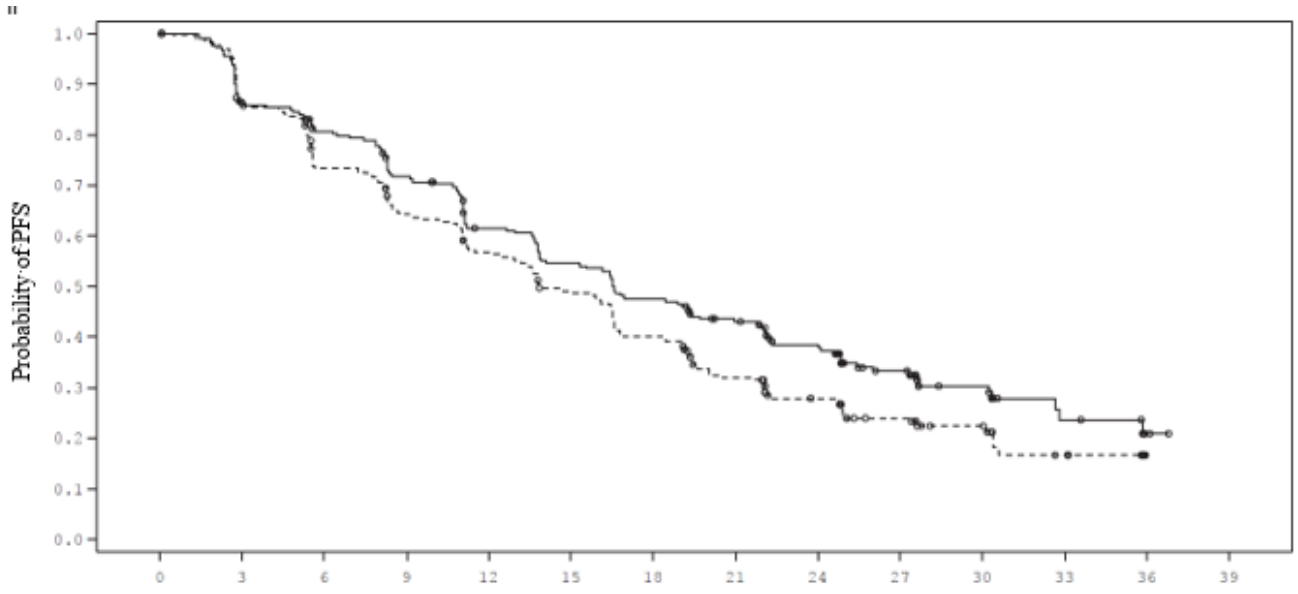
Consistent results were observed across the majority of pre-specified patient subgroups. For the subgroup of patients with disease limited to non-visceral metastasis (n=208), the HR was 0.592 (95% CI: 0.419, 0.837) for the fulvestrant arm compared to the anastrozole arm. For the subgroup of patients with visceral metastasis (n=254), the HR was 0.993 (95% CI: 0.740, 1.331) for the fulvestrant arm compared to the anastrozole arm. The efficacy results of the FALCON study are presented in Table 4 and Figure 1.

Table 4 Summary of results of the primary efficacy endpoint (PFS) and key secondary efficacy endpoints (Investigator Assessment, Intent-To-Treat Population) – FALCON study

	Fulvestrant 500 mg (N=230)	Anastrozole 1 mg (N=232)
Progression-Free survival		
Number of PFS Events (%)	143 (62.2%)	166 (71.6%)
PFS Hazard ratio (95% CI) and p-value	HR 0.797 (0.637 – 0.999) p = 0.0486	
PFS Median [months (95% CI)]	16.6 (13.8, 21.0)	13.8 (12.0, 16.6)
Number of OS Events*	67 (29.1%)	75 (32.3%)
OS Hazard Ratio (95% CI) and p-value	HR 0.875 (0.629 – 1.217) p = 0.4277	
ORR**	89 (46.1%)	88 (44.9%)
ORR Odds Ratio (95% CI) and p-value	OR 1.074 (0.716 – 1.614) p = 0.7290	
Median DoR (months)	20.0	13.2
CBR	180 (78.3%)	172 (74.1%)
CBR Odds Ratio (95% CI) and p-value	OR 1.253 (0.815 – 1.932) p = 0.3045	

*(31% maturity)-not final OS analysis
**for patients with measurable disease

Figure 1 Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment, Intent-To-Treat Population) – FALCON Study



Time from randomisation (months)

Treatment ——— Fulvestrant 500 mg (N=230) Anastrozole 1 mg (N=232)

Number of patients at risk

FUL500	230	187	171	150	124	110	96	81	63	44	24	11	2	0
ANAS1	232	194	162	139	120	102	84	60	45	31	22	10	0	0

Two phase-3 clinical trials were completed in a total of 851 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. Seventy seven percent (77%) of the study population had estrogen receptor positive breast cancer. These trials compared the safety and efficacy of monthly administration of fulvestrant 250 mg versus the daily administration of 1 mg anastrozole (aromatase inhibitor). Overall, fulvestrant at the 250 mg monthly dose was at least as effective as anastrozole in terms of progression-free survival, objective response, and time to death. There were no statistically significant differences in any of these endpoints between the two treatment groups. Progression-free survival was the primary endpoint. Combined analysis of both trials showed that 83% of patients who received fulvestrant progressed, compared with 85% of patients who received anastrozole. Combined analysis of both trials showed the hazard ratio of fulvestrant 250 mg to anastrozole for progression-free survival was 0.95 (95% CI 0.82 to 1.10). The objective response rate for fulvestrant 250 mg was 19.2% compared with 16.5% for anastrozole. The median time to death was 27.4 months for patients treated with fulvestrant and 27.6 months for patients treated with anastrozole. The hazard ratio of fulvestrant 250 mg to anastrozole for time to death was 1.01 (95% CI 0.86 to 1.19).

Combination therapy with palbociclib
A Phase 3, international, randomised, double-blind, parallel-group, multicentre study of fulvestrant 500 mg plus palbociclib 125 mg versus fulvestrant 500 mg plus placebo was conducted in women with HR-positive, HER2-negative locally advanced breast cancer not amenable to resection or radiation therapy with curative intent or metastatic breast cancer, regardless of their menopausal status, whose disease progressed after prior endocrine therapy in the (neo) adjuvant or metastatic setting.

A total of 521 pre/peri- and postmenopausal women who had progressed on or within 12 months from completion of adjuvant endocrine therapy on or within 1 month from prior endocrine therapy for advanced disease, were randomised 2:1 to fulvestrant plus palbociclib or fulvestrant plus placebo and stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri- versus postmenopausal), and presence of visceral metastases. Pre/perimenopausal women received the LHRH agonist goserelin. Patients with advanced/metastatic, symptomatic, visceral spread, that were at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement), were not eligible for enrolment into the study.

Patients continued to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. Crossover between treatment arms was not allowed.

Patients were well matched for baseline demographics and prognostic characteristics between the fulvestrant plus palbociclib arm and the fulvestrant plus placebo arm. The median age of patients enrolled in this study was 57 years (range 29, 88). In each treatment arm the majority of patients were White, had documented sensitivity to prior hormonal therapy, and were postmenopausal. Approximately 20% of patients were pre/perimenopausal. All patients had received prior systemic therapy and most patients in each treatment arm had received a previous chemotherapy regimen for their primary diagnosis. More than half (62%) had an ECOG PS of 0, 60% had visceral metastases, and 60% had received more than 1 prior hormonal regimen for their primary diagnosis.

The primary endpoint of the study was investigator-assessed PFS evaluated according to RECIST 1.1. Supportive PFS analyses were based on an Independent Central Radiology Review. Secondary endpoints included OR, CBR, overall survival (OS), safety, and time-to-deterioration (TTD) in pain endpoint.

The study met its primary endpoint of prolonging investigator-assessed PFS at the interim analysis conducted on 82% of the planned PFS events; the results crossed the pre-specified Haybittle-Peto

efficacy boundary (α=0.00135), demonstrating a statistically significant prolongation in PFS and a clinically meaningful treatment effect. A more mature update of efficacy data is reported in Table 5.

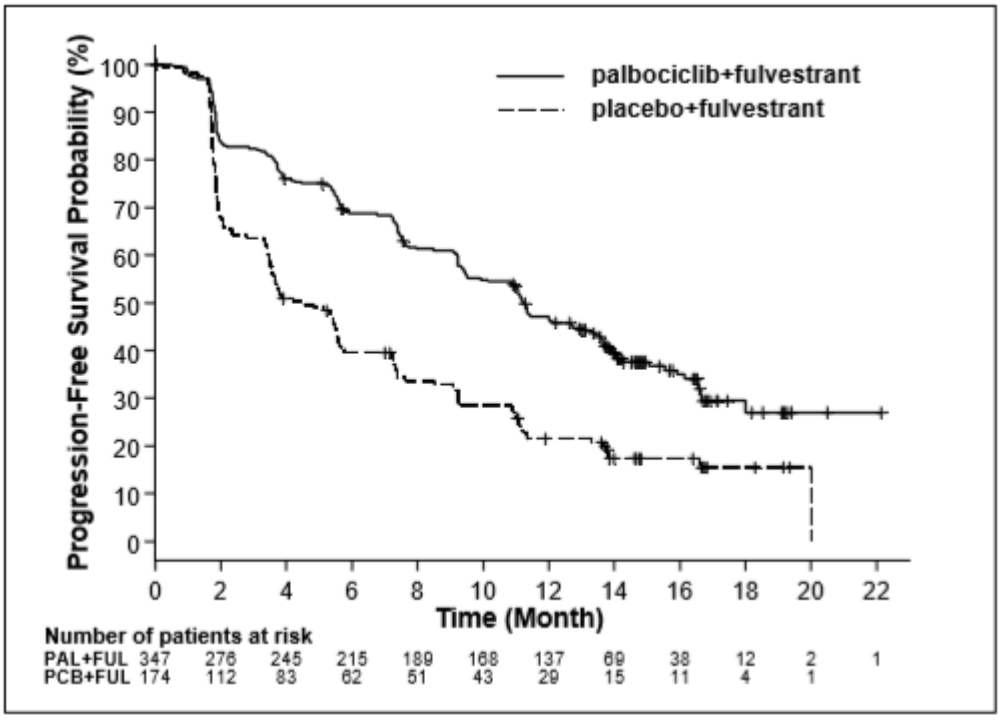
After a median follow-up time of 45 months, the final OS analysis was performed based on 310 events (60% of randomised patients). A 6.9-month difference in median OS in the palbociclib plus fulvestrant arm compared with the placebo plus fulvestrant arm was observed; this result was not statistically significant at the prespecified significance level of 0.0235(1-sided). In the placebo plus fulvestrant arm, 15.5% of randomised patients received palbociclib and other CDK inhibitors as post-progression subsequent treatments.
The results from the investigator-assessed PFS and final OS data from PALOMA3 study are presented in Table5. The relevant Kaplan-Meier plots are shown in Figures 2 and 3, respectively.

Table 5 Efficacy results – PALOMA3 study (Investigator assessment, intent-to-treat population)

	Updated Analysis (23 October 2015 cut-off)	
	Fulvestrant plus palbociclib (N=347)	**Fulvestrant plus placebo (N=174)**
Progression-Free Survival		
Median [months (95% CI)]	11.2 (9.5, 12.9)	4.6 (3.5, 5.6)
Hazard ratio (95% CI) and p-value	0.497 (0.398, 0.620), p <0.000001	
Secondary end points*		
OR [% (95%CI)]	26.2 (21.7, 31.2)	13.8 (9.0, 19.8)
OR (measurable disease) [% (95% CI)]	33.7 (28.1, 39.7)	17.4 (11.5, 24.8)
CBR [% (95% CI)]	68.0 (62.8, 72.9)	39.7 (32.3, 47.3)
Final overall survival (OS) (13April 2018 cutoff)		
Number of events (%)	201 (57.9)	109 (62.6)
Median [months (95% CI)]	34.9 (28.8, 40.0)	28.0 (23.6, 34.6)
Hazard ratio (95% CI) and p-value†	0.814 (0.644, 1.029) P=0.0429†	

CBR=clinical benefit response; CI=confidence interval; N=number of patients; OR=objective response
Secondary endpoint results are based on confirmed and unconfirmed responses according to RECIST 1.1.
* Not statistically significant.
†1-sided p-value from the log-rank test stratified by the presence of visceral metastases and sensitivity to prior endocrine therapy per randomisation.

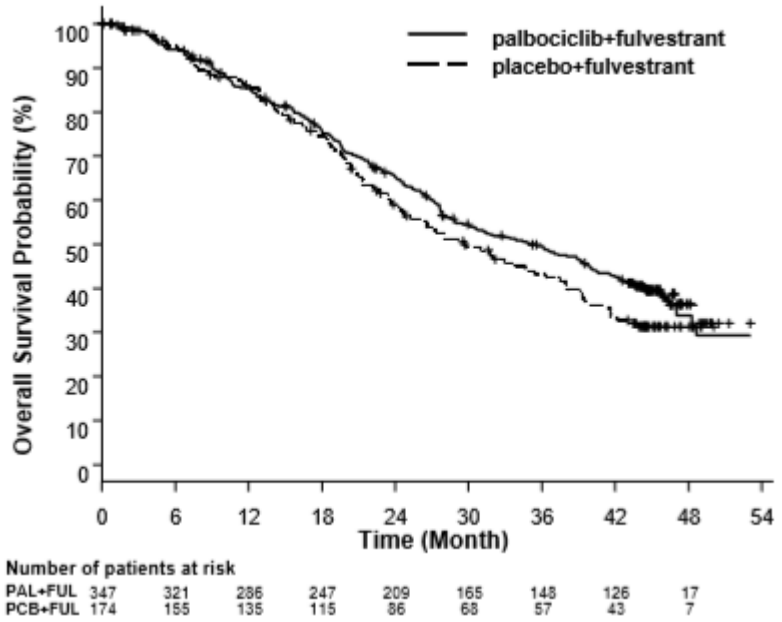
Figure 2 Kaplan-Meier plot of progression-free survival (investigator assessment, intent- to-treat population) – PALOMA3 study (23 October2015 cutoff)



FUL=fulvestrant; PAL=palbociclib; PCB=placebo.

A reduction in the risk of disease progression or death in the fulvestrant plus palbociclib arm was observed in all individual patient subgroups defined by stratification factors and baseline characteristics. This was evident for pre/perimenopausal women (HR of 0.46 [95% CI: 0.28, 0.75]) and postmenopausal women (HR of 0.52 [95% CI: 0.40, 0.66]) and patients with visceral site of metastatic disease (HR of 0.50 [95% CI: 0.38, 0.65]) and non-visceral site of metastatic disease (HR of 0.48 [95% CI: 0.33, 0.71]). Benefit was also observed regardless of lines of prior therapy in the metastatic setting, whether 0 (HR of 0.59 [95% CI: 0.37, 0.93]), 1 (HR of 0.46 [95% CI: 0.32, 0.64]), 2 (HR of 0.48 [95% CI: 0.30, 0.76]), or ≥3 lines (HR of 0.59 [95% CI: 0.28, 1.22]).

Figure 3. Kaplan-Meier plot of overall survival (intent-to-treat population) – PALOMA3 study (13 April 2018 cut off)



FUL= fulvestrant; PAL= palbociclib; PCB= placebo.

Additional efficacy measures (OR and TTR) assessed in the sub-groups of patients with or without visceral disease are displayed in Table 6.

Table 6 Efficacy results in visceral and non-visceral disease from PALOMA3 study (intent-to-treat population)

	Visceral Disease		Non-visceral Disease	
	Fulvestrant plus palbociclib (N=206)	**Fulvestrant plus placebo (N=105)**	**Fulvestrant plus palbociclib (N=141)**	**Fulvestrant plus placebo (N=69)**
OR [% (95% CI)]	35.0 (28.5, 41.9)	13.3 (7.5, 21.4)	13.5 (8.3, 20.2)	14.5 (7.2, 25.0)
TTR*, Median [months (range)]	3.8 (3.5, 16.7)	5.4 (3.5, 16.7)	3.7 (1.9, 13.7)	3.6 (3.4, 3.7)

*Response results based on confirmed and unconfirmed responses.

N=number of patients; CI=confidence interval; OR= objective response; TTR=time to first tumour response.

Patient-reported symptoms were assessed using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and its Breast Cancer Module (EORTC QLQ-BR23). A total of 335 patients in the fulvestrant plus palbociclib arm and 166 patients in the fulvestrant plus placebo arm completed the questionnaire at baseline and at least 1 post-baseline visit.

Time-to-Deterioration was pre-specified as time between baseline and first occurrence of ≥10 points increase from baseline in pain symptom scores. Addition of palbociclib to fulvestrant resulted in a symptom benefit by significantly delaying Time-to-Deterioration in pain symptom compared with fulvestrant plus placebo (median 8.0 months versus 2.8 months; HR of 0.64 [95% CI: 0.49, 0.85]; p<0.001.

Effects on the postmenopausal endometrium

Preclinical data do not suggest a stimulatory effect of fulvestrant on the postmenopausal endometrium (see section 5.3). A 2-week study in healthy postmenopausal volunteers treated with 20 micrograms per day ethinylestradiol showed that pre-treatment with fulvestrant 250 mg resulted in significantly reduced stimulation of the postmenopausal endometrium, compared to pre-treatment with placebo, as judged by ultrasound measurement of endometrium thickness.

Neoadjuvant treatment for up to 16 weeks in breast cancer patients treated with either fulvestrant 500 mg or fulvestrant 250 mg did not result in clinically significant changes in endometrial thickness, indicating a lack of agonist effect. There is no evidence of adverse endometrial effects in the breast cancer patients studied. No data are available regarding endometrial morphology.

In two short-term studies (1 and 12 weeks) in premenopausal patients with benign gynaecologic disease, no significant differences in endometrial thickness were observed by ultrasound measurement between fulvestrant and placebo groups.

Effects on bone
There are no long-term data on the effect of fulvestrant on bone. Neoadjuvant treatment for up to 16 weeks in breast cancer patients with either fulvestrant 500 mg or fulvestrant 250 mg did not result in clinically significant changes in serum bone-turnover markers.

Paediatric population
Fulvestrant is not indicated for use in children. The European Medicines Agency has waived the obligation to submit the results of studies with fulvestrant in all subsets of the paediatric population in breast cancer (see section 4.2 for information on paediatric use).

An open-label phase 2 study investigated the safety, efficacy and pharmacokinetics of fulvestrant in 30 girls aged 1 to 8 years with Progressive Precocious Puberty associated with McCune Albright Syndrome (MAS). The paediatric patients received 4 mg/kg monthly intramuscular dose of fulvestrant. This 12-month study investigated a range of MAS endpoints and showed a reduction in the frequency of vaginal bleeding and a reduction in the rate of bone age advancement. The steady-state trough concentrations of fulvestrant in children in this study were consistent with that in adults (see section 5.2). There were no new safety concerns arising from this small study, but 5-year data are yet not available.

5.2 Pharmacokinetic properties

Absorption
After administration of fulvestrant long-acting intramuscular injection, fulvestrant is slowly absorbed and maximum plasma concentrations (C_{max}) are reached after about 5 days. Administration of fulvestrant 500 mg regimen achieves exposure levels at, or close to, steady state within the first month of dosing (mean [CV]: AUC 475 [33.4%] ng.days/ml, C_{max} 25.1 [35.3%] ng/ml, C_{min} 16.3 [25.9%] ng/ml, respectively). At steady state, fulvestrant plasma concentrations are maintained within a relatively narrow range with up to an approximately 3-fold difference between maximum and trough concentrations. After intramuscular administration, the exposure is approximately dose-proportional in the dose range 50 to 500mg.

Distribution
Fulvestrant is subject to extensive and rapid distribution. The large apparent volume of distribution at steady state (Vd_{ss}) of approximately 3 to 5 l/kg suggests that distribution is largely extravascular.
Fulvestrant is highly (99%) bound to plasma proteins. Very low-density lipoprotein (VLDL), low density lipoprotein (LDL), and high-density lipoprotein (HDL) fractions are the major binding components. No interaction studies were conducted on competitive protein binding. The role of sex hormone-binding globulin (SHBG) has not been determined.

Biotransformation
The metabolism of fulvestrant has not been fully evaluated but involves combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids. Identified metabolites (includes 17-ketone, sulphone, 3-sulphate, 3- and 17-glucuronide metabolites) are either less active or exhibit similar activity to fulvestrant in anti-estrogen models. Studies using human liver preparations and recombinant human enzymes indicate that CYP3A4 is the only P450 isoenzyme involved in the oxidation of fulvestrant; however, non-P450 routes appear to be more predominant in vivo. In vitro data suggest that fulvestrant does not inhibit CYP450 isoenzymes.

Elimination
Fulvestrant is eliminated mainly in metabolised form. The major route of excretion is via the faeces, with less than 1% being excreted in the urine. Fulvestrant has a high clearance, 11±1.7 ml/min/kg, suggesting a high hepatic extraction ratio. The terminal half-life ($t_{1/2}$) after intramuscular administration is governed by the absorption rate and was estimated to be 50 days.

Special populations
In a population pharmacokinetic analysis of data from phase 3studies, no difference in fulvestrant's pharmacokinetic profile was detected with regard to age (range 33 to 89 years), weight (40-127 kg) or race.

Renal impairment
Mild to moderate impairment of renal function did not influence the pharmacokinetics of fulvestrant to any clinically relevant extent.

Hepatic impairment
The pharmacokinetics of fulvestrant has been evaluated in a single-dose clinical trial conducted in subjects with mild to moderate hepatic impairment (Child-Pugh class A and B). A high dose of a shorter duration intramuscular injection formulation was used. There was up to about 2.5-fold increase in AUC in women with hepatic impairment compared to healthy subjects. In patients administered fulvestrant, an increase in exposure of this magnitude is expected to be well tolerated. Women with severe hepatic impairment (Child-Pugh class C) were not evaluated.

Paediatric population
The pharmacokinetics of fulvestrant has been evaluated in a clinical trial conducted in 30 girls with Progressive Precocious Puberty associated with McCune Albright Syndrome (see section 5.1). The paediatric patients were aged 1 to 8 years and received 4 mg/kg monthly intramuscular dose of fulvestrant. The geometric mean (standard deviation) steady state trough concentration (Cmin,ss) and AUCss was 4.2 (0.9) ng/mL and 3680 (1020) ng*hr/mL, respectively. Although the data collected were limited, the steady-state trough concentrations of fulvestrant in children appear to be consistent with those in adults.

5.3 Preclinical safety data

The acute toxicity of fulvestrant is low.

The reference medicinal product and other formulations of fulvestrant were well tolerated in animal species used in multiple dose studies. Local reactions, including myositis and granulomata at the injection site were attributed to the vehicle but the severity of myositis in rabbits increased with fulvestrant, compared to the saline control. In toxicity studies with multiple intramuscular doses of fulvestrant in rats and dogs, the anti- estrogenic activity of fulvestrant was responsible for most of the effects seen, particularly in the female reproductive system, but also in other organs sensitive to hormones in both sexes. Arteritis involving a range of different tissues was seen in some dogs after chronic (12 months) dosing.

In dog studies following oral and intravenous administration, effects on the cardiovascular system (slight elevations of the S-T segment of the ECG [oral], and sinus arrest in one dog [intravenous]) were seen. These occurred at exposure levels higher than in patients (C_{max} >15 times) and are likely to be of limited significance for human safety at the clinical dose.

Fulvestrant showed no genotoxic potential.

Fulvestrant showed effects upon reproduction and embryo/foetal development consistent with its anti- estrogenic activity, at doses similar to the clinical dose. In rats, a reversible reduction in female fertility and embryonic survival, dystocia and an increased incidence of foetal abnormalities including tarsal flexure were observed. Rabbits given fulvestrant failed to maintain pregnancy. Increases in placental weight and post-implantation loss of foetuses were seen. There was an increased incidence of foetal variations in rabbits (backwards displacement of the pelvic girdle and 27 pre-sacral vertebrae).

A two-year oncogenicity study in rats (intramuscular administration of fulvestrant) showed increased incidence of ovarian benign granulosa cell tumours in female rats at the high dose, 10 mg/rat/15 days and an increased incidence of testicular Leydig cell tumours in males. In a two-year mouse oncogenicity study (daily oral administration) there was an increased incidence of ovarian sex cord stromal tumours (both benign and malignant) at doses of 150 and 500 mg/kg/day. At the no-effect level for these findings, systemic exposure levels (AUC) were, in rats, approximately 1.5-fold the expected human exposure levels in females and 0.8-fold in males, and in mice, approximately 0.8-fold the expected human exposure levels in both males and females. Induction of such tumours is consistent with pharmacology-related endocrine feedback alterations in gonadotropin levels caused by anti-estrogens in cycling animals. Therefore these findings are not considered to be relevant to the use of fulvestrant in postmenopausal women with advanced breast cancer.

Environmental Risk Assessment (ERA) Environmental risk assessment studies have shown that fulvestrant may have potential to cause adverse effects to the aquatic environment (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol (96%)
Benzyl alcohol (E1519)
Benzyl benzoate
Castor oil, refined

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store and transport refrigerated (2°C-8°C).

Temperature excursions outside 2°C-8°C should be limited. This includes avoiding storage at temperatures exceeding 30°C, and not exceeding a 28 day period where the average storage temperature for the product is below 25°C (but above 2°C-8°C). After temperature excursions, the product should be returned immediately to the recommended storage conditions (store and transport refrigerated 2°C-8°C). Temperature excursions have a cumulative effect on the product quality and the 28 daytime period must not be exceeded over the duration of the 2-year shelf life of fulvestrant (see section 6.3). Exposure to temperatures below 2°C will not damage the product providing it is not stored below -20°C.

Store the pre-filled syringe in the original package in order to protect from light.

6.5 Nature and contents of container

The pre-filled syringe presentation consists of:

One clear type 1 glass pre-filled syringe with polystyrene plunger rod and elastomeric plunger stopper, fitted with a Plastic Rigid Tip cap, containing 5 ml fulvestrant solution for injection.
A safety needle (BD SafetyGlide) for connection to the barrel is also provided.

Or

Two clear type 1 glass pre-filled syringes with polystyrene plunger rod and elastomeric plunger stopper, fitted with a Plastic Rigid Tip cap, each containing 5 ml fulvestrant solution for injection. Two safety needles (BD SafetyGlide) for connection to each barrel are also provided.

Or

Six clear type 1 glass pre-filled syringes with polystyrene plunger rod and elastomeric plunger stopper, fitted with a Plastic Rigid Tip cap, each containing 5 ml fulvestrant solution for injection. Six safety needles (BD SafetyGlide) for connection to each barrel are also provided.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

Instructions for administration

Administer the injection according to the local guidelines for performing large volume intramuscular injections.

NOTE: Due to the proximity of the underlying sciatic nerve, caution should be taken if administering fulvestrant at the dorsogluteal injection site (see section 4.4).

Warning - Do not autoclave safety needle (BD SafetyglideTM Safety Hypodermic Needle) before use. Hands must remain behind the needle at all times during use and disposal.

For each of the two syringes:

- Remove glass syringe barrel from tray and check that it is not damaged.
- Peel open the safety needle (SafetyGlide) outer packaging.
- Parenteral solutions must be inspected visually for particulate matter and discolouration prior to administration.

- Hold the syringe upright on the ribbed part (C). With the other hand, take hold of the cap (A) and carefully twist the plastic rigid tip cap in anticlockwise direction. (see Figure 1):

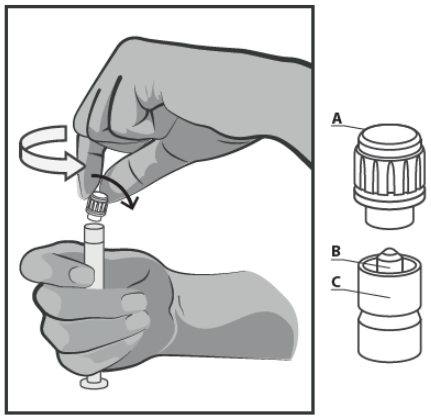


Figure 1

- Remove the cap (A) in a straight upward direction. To maintain sterility do not touch the syringe tip (B) (see Figure 2).

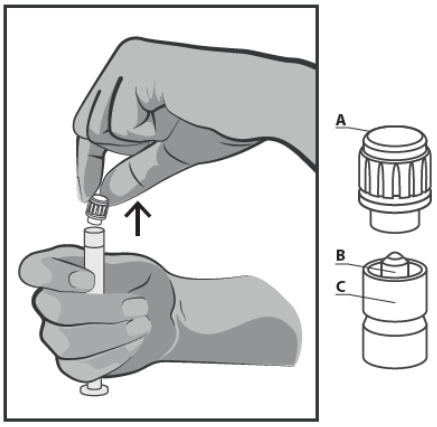


Figure 2

- Attach the safety needle to the Luer-Lok and twist until firmly seated (see Figure 3).
- Check that the needle is locked to the Luer connector before moving out of the vertical plane.
- Pull shield straight off needle to avoid damaging needle point.
- Transport filled syringe to point of administration.
- Remove needle sheath.
- Expel excess gas from the syringe.

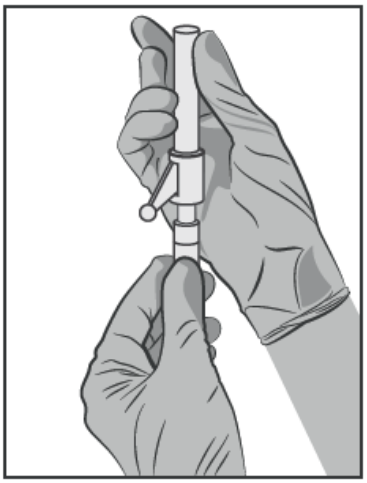


Figure 3

- Administer intramuscularly slowly (1-2 minutes/injection) into the buttock (gluteal area). For user convenience, the needle bevel- up position is oriented to the lever arm (see Figure 4).

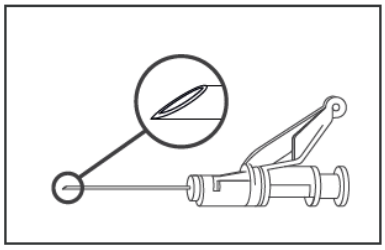


Figure 4

- After injection, immediately apply a single-finger stroke to the activation assisted lever arm to activate the shielding mechanism (see Figure 5).

NOTE: Activate away from self and others. Listen for click and visually confirm needle tip is fully covered.

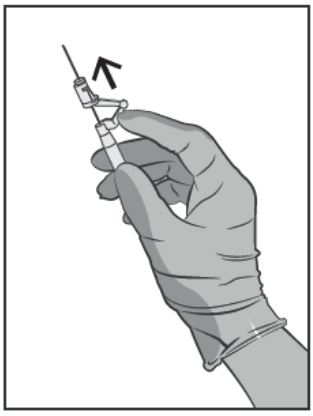


Figure 5

Disposal
Pre-filled syringes are for single use **only**.

This medicine may pose a risk to the aquatic environment. Any unused medicinal product or waste material should be disposed of in accordance with local requirements (see section 5.3).

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

*Chemical Works of Ge*deon Richter PLC
Gyomroi Ut 19-21
1103 Budapest X
Hongarije

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 126293

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 6 oktober 2020

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft rubriek 1: 23 december 2020