

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fulvestrant Rowex 250mg/5ml solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe contains 250 mg fulvestrant in 5 ml solution.

Excipient(s) with known effect

- Ethanol (96%) (100mg/ml)
- Benzyl alcohol (100mg/ml)
- Benzyl benzoate (150mg/ml)

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

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Fulvestrant Rowex 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 Rowex 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 studies with Fulvestrant Rowex (see section 4.8). This should be taken into consideration when prescribing Fulvestrant Rowex 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 Rowex (either as monotherapy or in combination with palbociclib) have not been studied in patients with critical visceral disease.

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

Interference with oestradiol antibody assays

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

Paediatric population

Fulvestrant Rowex 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).

Excipients

This medicinal product contains ethanol, benzyl alcohol and benzyl benzoate.

This medicinal product contains 1000 mg of alcohol (ethanol 96%) per given dose, which is equivalent to 100 mg/ml (10% w/v). The amount per given dose of this medicinal product is equivalent to less than 24 ml beer or 10 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

This medicinal product contains 1000 mg benzyl alcohol per given dose, which is equivalent to 100 mg/ml. Benzyl alcohol may cause allergic reactions.

Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gaspings syndrome") in young children.

Increased risk due to accumulation in young children.

High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

This medicinal product contains 1500 mg benzyl benzoate per given dose, which is equivalent to 150 mg/ml. Benzyl benzoate may increase jaundice (yellowing of the skin and eyes) in new born babies (up to 4 weeks old). Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

4.5 Interaction with other medicinal products and other forms of interactions

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 child-bearing potential should use effective contraception during treatment with fulvestrant and for 2 years after the last dose.

Pregnancy

Fulvestrant Rowex 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 Rowex, the patient must be informed of the potential hazard to the foetus and potential risk for loss of pregnancy.

Breast-feeding

Breastfeeding must be discontinued during treatment with Fulvestrant Rowex. 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 Rowex on fertility in humans has not been studied.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Monotherapy

This section provides information based on all adverse reactions from clinical studies, post-marketing studies or spontaneous reports. In the pooled dataset of fulvestrant monotherapy, the most frequently reported adverse reactions were 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 500mg with fulvestrant 250mg [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 Table 1 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 ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ 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	Increased 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
Musculoskeletal and connective tissue disorders	Very common	Joint and musculoskeletal pain ^d
	Common	Back pain ^a
Reproductive system and breast disorders	Common	Vaginal haemorrhage ^e
	Uncommon	Vaginal moniliasis ^f , leukorrhoea ^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, 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 ($\geq 20\%$) 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 ($\geq 2\%$) Grade ≥ 3 adverse reactions were neutropenia, leukopenia, infections, anaemia, 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		Fulvestrant+ placebo	
	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n(%)	Grade ≥ 3 n (%)
Infections and infestations				
<i>Very common</i>				
Infections ^b	188 (54.5)	19 (5.5)	60 (34.9)	6 (3.5)
Blood and lymphatic system disorders				
<i>Very common</i>				
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
<i>Uncommon</i>				
Febrile neutropenia	3 (0.9)	3 (0.9)	0	0
Metabolism and nutrition disorders				
<i>Very common</i>				
Decreased appetite	60 (17.4)	4 (1.2)	18 (10.5)	1 (0.6)
Nervous system disorders				
<i>Common</i>				
Dysgeusia	27 (7.8)	0	6 (3.5)	0
Eye disorders				
<i>Common</i>				
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				
<i>Common</i>				
Epistaxis	25 (7.2)	0	4 (2.3)	0
Gastrointestinal disorders				
<i>Very common</i>				
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				
<i>Very common</i>				
Alopecia	67 (19.4)	NA	11 (6.4)	NA
Rash ^h	63 (18.3)	3 (0.9)	10 (5.8)	0
<i>Common</i>				
Dry skin	28 (8.1)	0	3 (1.7)	0
General disorders and administration site conditions				
<i>Very common</i>				
Fatigue	152 (44.1)	9 (2.6)	54 (31.4)	2 (1.2)
Pyrexia	47 (13.6)	1 (0.3)	10 (5.8)	0
<i>Common</i>				
Asthenia	27 (7.8)	1 (0.3)	13 (7.6)	2 (1.2)
Investigations				
<i>Very common</i>				
AST increased	40 (11.6)	11 (3.2)	13 (7.6)	4 (2.3)
<i>Common</i>				
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 \geq 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:

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-oestrogens, ATC code: L02BA03

Mechanism of action and pharmacodynamic effects

Fulvestrant is a competitive oestrogen receptor (ER) antagonist with an affinity comparable to oestradiol. Fulvestrant blocks the trophic actions of oestrogens without any partial agonist (oestrogen-like) activity. The mechanism of action is associated with down-regulation of oestrogen receptor protein levels.

Clinical studies 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 oestrogen 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 safety and efficacy in advanced breast cancer

Monotherapy

A phase III clinical study 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 study compared the efficacy and safety of fulvestrant 500 mg (n=362) with fulvestrant 250 mg (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 500mg (N=362)	Fulvestrant 250mg (N=374)	Comparison between groups (Fulvestrant 500mg/ Fulvestrant 250mg)		
PFS	K-M median in months; hazard ratio			Hazard ratio	95% CI	p-value
All Patients		6.5	5.5	0.80	0.68, 0.94	0.006
- AE sub group (n = 423)		8.6	5.8	0.76	0.62, 0.94	0.013
- AI sub group (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 sub group (n = 423)		30.6	23.9	0.79	0.63, 0.99	0.038 ^c
- AI sub group (n = 313) ^a		24.1	20.8	0.86	0.67, 1.11	0.241 ^c
Variable	Type of estimate; treatment	Fulvestrant 500mg (N=362)	Fulvestrant 250mg (N=374)	Comparison between groups (Fulvestrant500mg/		

	comparison			Fulvestrant250mg)		
ORR ^d	% of patients with OR; absolute difference in %			Absolute difference in %	95% CI	
All Patients		13.8	14.6	-0.8	-5.8, 6.3	
- AE sub group (n = 296)		18.1	19.1	-1.0	-8.2, 9.3	
- AI sub group (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 sub group (n = 423)		52.4	45.1	7.3	-2.2, 16.6	
- AI sub group (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 (ie, 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 \geq 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-positivelocally advancedor metastatic breast cancer who had not previously been treated with any hormonal therapy. A total of 462 patients were randomised 1:1sequentially to receive either fulvestrant 500 mg or anastrozole 1mg.

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 aprior 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), theHR 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.

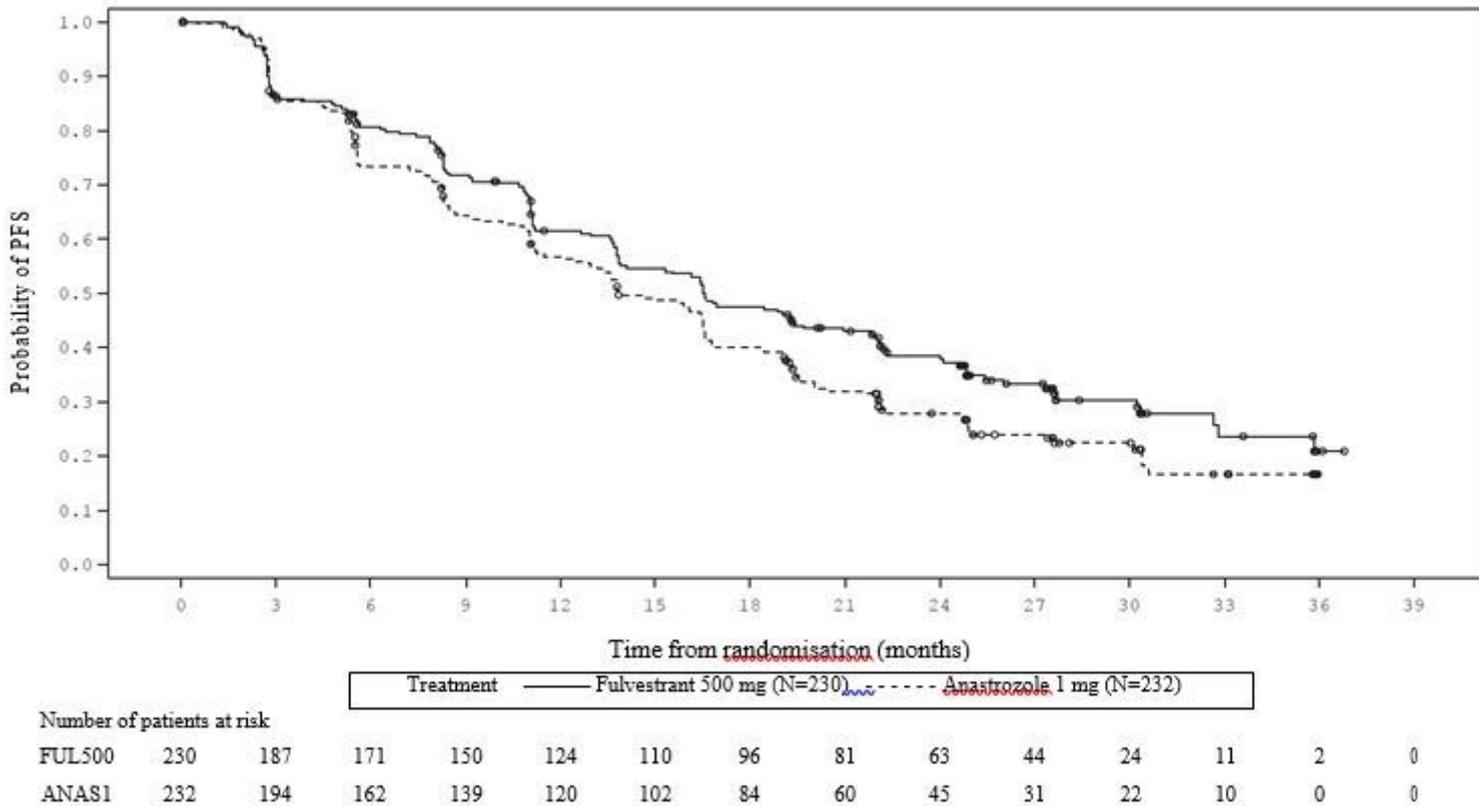
Table 4 Summary of results of the primary efficacy endpoint (PFS) and key secondary efficacy endpoints (Investigator Assessment, Intent-To-Treat Population) FALCON study

	Fulvestrant 500mg (N=230)	Anastrozole 1mg(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



Two Phase 3 clinical studies 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 studies 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 studies showed that 83% of patients who received Fulvestrant progressed, compared with 85% of patients who received anastrozole. Combined analysis of both studies 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 ($\alpha=0.00135$), 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 Table 5. 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,		

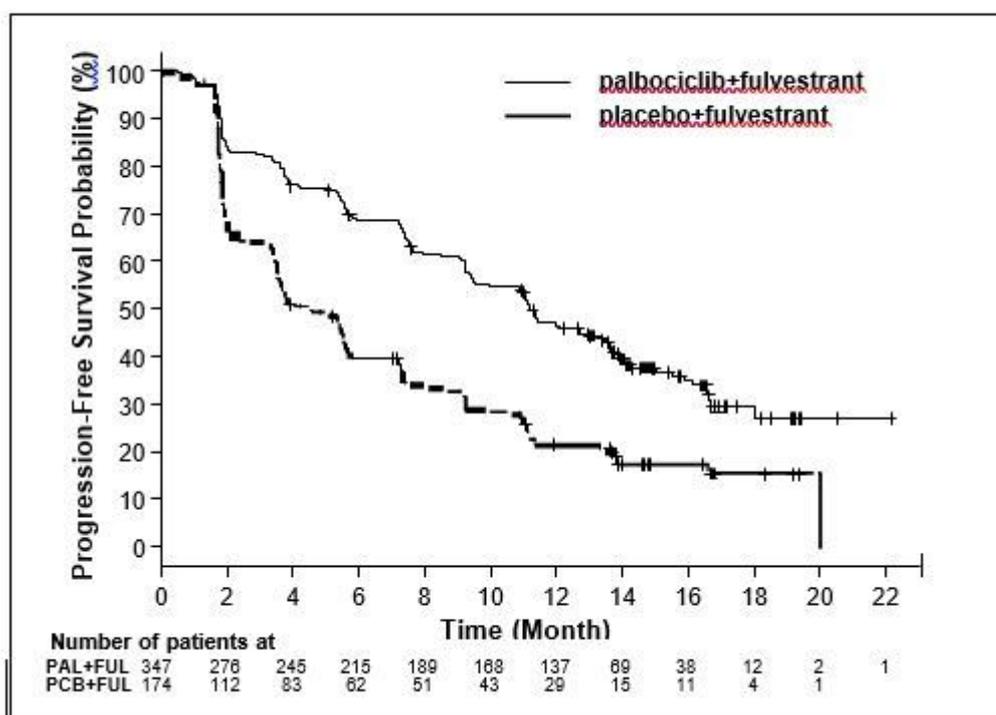
		0.620), p <0.000001		
Secondary end points*				
OR [% (95% CI)]		26.2 (21.7, 31.2)		13.8 (9.0, 19.8)
OR (measurable disease) [% (95% CI)]		33.7 (28.1, 39.7)		17.4 (11.5, 24.8)
CBR [% (95% CI)]		68.0 (62.8, 72.9)		39.7 (32.3, 47.3)
Final overall survival (OS) (13 April 2018 cutoff)				
Number of events (%)	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.

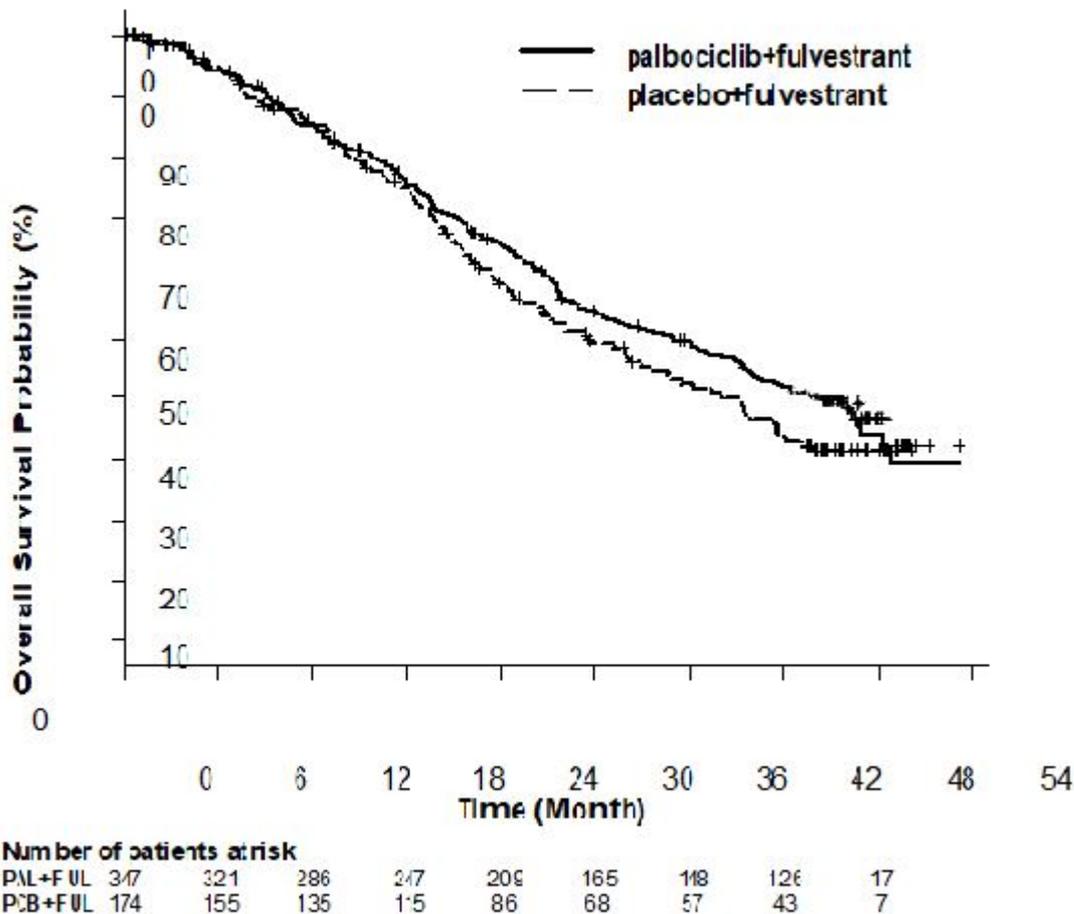
Figure 2. Kaplan-Meier plot of progression-free survival (investigator assessment, intent-to-treat population) – PALOMA3 study(23 October 2015 cutoff)



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	Fulvestrant plus placebo	Fulvestrant plus palbociclib	Fulvestrant plus placebo
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	3.8	5.4	3.7	3.6
[months (range)]	(3.5, 16.7)	(3.5, 16.7)	(1.9, 13.7)	(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 II 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 [35.1%] 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 500 mg.

Distribution

Fulvestrant is subject to extensive and rapid distribution. The large apparent volume of distribution at steady state ($V_{d,ss}$) 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-oestrogen 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 III studies, 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 study conducted in women 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 subjects with hepatic impairment compared to healthy women. 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 study 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 ($C_{min,ss}$) and AUC_{ss} 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.

Fulvestrant 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-oestrogenic 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-oestrogenic 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 per cent)
Benzyl alcohol
Benzyl benzoate
Castor oil

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

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Fulvestrant Rowex is provided in one or two single-use pre-filled syringes, consisting of a siliconised type 1 glass barrel fitted with: a tamper evident closure connector, a siliconised brombutyl rubber plunger, a bromobutyl/synthetic isoprene rubber tip-cap, a polystyrene plunger rod, a polypropylene back stop. Additionally to each pre-filled syringe a sterile needle is provided.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handlingInstructions 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 Rowex at the dorsogluteal injection site (see section 4.4).

Warning - Do not autoclave safety needle before use. Hands must remain behind the needle at all times during use and disposal.

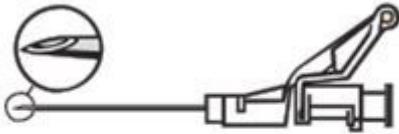
Syringes are supplied with safety needle BD SafetyGlide® or Terumo SurGuard®.

Instructions for safety needle BD SafetyGlide®For each of the two syringes:

- Carefully remove the needle and syringe from the packaging.
- Remove the protective cap from the tip of the syringe barrel.
- Peel open the safety needle (BD SafetyGlide) outer packaging. Attach the safety needle to the Luer-Lock.
- Twist to lock the needle to the Luerconnector. Twist until firmly seated.
- Pull shield straight off needle to avoid damaging needle point.



- Remove needle sheath.
- While holding the syringe with the needle pointing upward, gently push in the plunger until the medicine is up to the top of the syringe. There should be no air within the barrel.
- Administer intramuscularly slowly (1-2 minutes/injection) into the buttock. For user convenience, the needle bevel- up position is oriented to the lever arm.
- After injection, immediately apply a single-finger stroke to the activation assisted lever arm to activate the shielding mechanism.

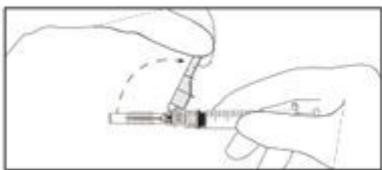
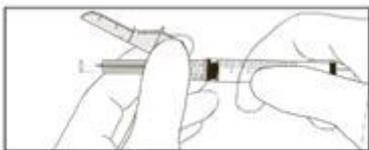


NOTE: Activate away from self and others. Listen for click and visually confirm needle tip is fully covered.

Instructions for safety needle Terumo SurGuard®

For each of the two syringes:

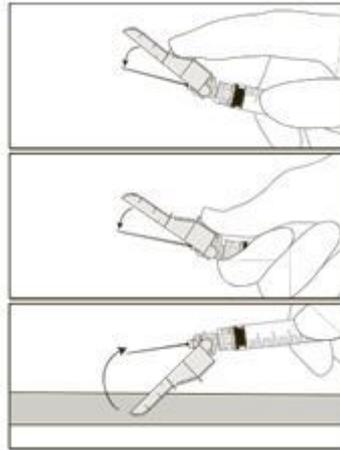
- Carefully remove the needle and syringe from the packaging.
- Remove the protective cap from the tip of the syringe barrel.



- Tighten the syringe to the needle using aseptic technique. Grip the base of the needle, not the sheath, and turn the syringe clockwise.
- Move the safety shield away from the needle and toward the syringe barrel to the angle shown. Then remove the needle cap.
- While holding the syringe with the needle pointing upward, gently push in the plunger until the medicine is up to the top of the syringe. There should be no air within the barrel.
- Administer intramuscularly slowly (1-2 minutes/injection) into the buttock.

- After completing the injection, remove the needle from the skin and use a one-handed technique to activate the safety mechanism using any of the three methods:

- **Finger activation**
- **Thumb activation**
- **Surface activation**



Activation is verified by an audible and/or tactile “click”, and can be visually confirmed. If uncertain that the safety shield is fully engaged, repeat this step.

Disposal

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

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

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/245/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 28th August 2015

10 DATE OF REVISION OF THE TEXT

January 2022