PRODUCT MONOGRAPH

Pr FULVESTRANT INJECTION

fulvestrant injection

50 mg/mL

Nonagonist Estrogen Receptor Antagonist

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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular injection	Pre-filled syringe injection 50 mg/mL	Alcohol 96%, benzyl alcohol, benzyl benzoate, refined castor oil

INDICATIONS AND CLINICAL USE

Fulvestrant Injection is indicated for the:

- treatment of estrogen receptor-positive, human epidermal growth receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in postmenopausal women not previously treated with endocrine therapy, or
- hormonal treatment of locally advanced or metastatic breast cancer in postmenopausal women, regardless of age, who have disease progression following prior anti-estrogen therapy.

Geriatrics:

No changes in dose are necessary for elderly patients.

Pediatrics:

Fulvestrant Injection is not recommended for use in the pediatric population, as safety and efficacy have not been established in this age group.

CONTRAINDICATIONS

- Patients with known hypersensitivity to fulvestrant or to any of the excipients. For a complete listing of ingredients, see the Dosage Forms, Composition and Packaging section of the Product Monograph.
- Pregnant or lactating women.

WARNINGS AND PRECAUTIONS

General

Fulvestrant is unlikely to impair the ability of patients to drive or operate machinery. However, during treatment with fulvestrant, asthenia has been reported, and caution should be observed by those patients who experience this symptom when driving or operating machinery.

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 Injection at the dorsogluteal injection site due to the proximity of the underlying sciatic nerve and large blood vessels (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Hematologic

Due to the route of administration (intramuscular injection), caution should be used before treating patients on anticoagulants or patients with bleeding diatheses or thrombocytopenia.

Hepatic

Fulvestrant is associated with elevated transaminase, bilirubin, and alkaline phosphatase levels. In some cases, discontinuation of treatment resulted in improvement of transaminase and bilirubin levels.

Post-hoc analysis of the pivotal CONFIRM study found 9 (1.2%) potential Hy's law cases which may be predictive of more severe hepatic events in the post-marketing setting.

Hepatic failure (in some cases fatal) has been reported in patients treated with fulvestrant.
There was no clear evidence of liver metastases in these case reports and the events had a clear temporal relationship with fulvestrant use; therefore a causal link between these events and fulvestrant could not be excluded (see ADVERSE REACTIONS). Liver function tests should be performed on a regular basis or when clinically indicated.

Immune

Hypersensitivity reactions including angioedema and urticaria may occur. These reactions may occur shortly after injection, or in one reported case of angioedema, several days after injection. Local injection site reactions (e.g. pruritus, urticaria) may occur even after prior uneventful injections, and have been reported to develop with time into a systemic allergic response (e.g. widespread urticaria). Fulvestrant therapy may need to be discontinued.

Musculoskeletal

There are no long-term data on the effect of fulvestrant on bone. Due to the mode of action of fulvestrant, there is a potential risk of osteoporosis. These data were not collected in the long term follow-up of the CONFIRM study.

Renal

Caution should be used before treating patients with creatinine clearance less than 30 mL/min.

Immunoassay Measurement of Serum Estradiol

Fulvestrant can interfere with estradiol measurement by immunoassay, resulting in falsely elevated estradiol levels (see DRUG INTERACTIONS, Drug-Laboratory Interactions).

Special Populations

Pregnant Women: Fulvestrant is contraindicated in pregnant women.

Fulvestrant can cause fetal harm if administered to a pregnant woman. Women of childbearing potential should use effective contraception during treatment with Fulvestrant Injection and for 2 years after the last dose.

If a patient becomes pregnant while receiving Fulvestrant Injection she should be apprised of the potential hazard to the fetus, or the potential risk for loss of pregnancy.

Nursing Women: Fulvestrant is contraindicated in lactating women.

Fulvestrant is found in rats' milk at levels significantly higher than those in rat plasma. It is not known if fulvestrant is excreted in human milk. However, since many drugs are excreted in human milk, and because of the potential for serious adverse reactions from Fulvestrant Injection in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug.

Pediatrics: Fulvestrant is not recommended for use in the pediatric population, as safety and efficacy have not been established in this age group.

Hepatic Impairment: Fulvestrant is metabolized primarily in the liver; thus, clearance may be reduced in women with hepatic impairment. Pharmacokinetic data show that the mean clearance is reduced 2.2 fold in women with moderate hepatic impairment in comparison to healthy women. The average AUC of fulvestrant in these women (Child-Pugh Category B) increased by approximately 70% compared to patients with normal hepatic function (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency). There are no efficacy and safety data available for fulvestrant in breast cancer patients with hepatic impairment.

Caution should be used with fulvestrant in patients with mild to moderate hepatic impairment. The potential risk/benefit to patients with moderate hepatic impairment should be carefully considered before administration of Fulvestrant Injection. Fulvestrant has not been investigated in women with severe (Child-Pugh Category C) hepatic impairment; therefore, it is not recommended for use in these patients.

Monitoring and Laboratory Tests

Liver function tests should be performed on a regular basis or when clinically indicated (see WARNINGS AND PRECAUTIONS, Hepatic).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Fulvestrant 500 mg was well tolerated with a similar tolerability profile to fulvestrant 250 mg. Adverse drug reactions for which there is evidence of an increased incidence for fulvestrant 500 mg include injection site reactions and hypersensitivity reactions (predominantly pruritus). An increased incidence of injection site reactions and hypersensitivity reactions, such as pruritus, is consistent with the increased number of injections required for the fulvestrant 500 mg dose regimen compared to fulvestrant 250 mg.

Following review of clinical trial data, a number of adverse drug reactions (ADRs) were identified for fulvestrant 500 mg, where a causal link has been established between the ADR and fulvestrant treatment. These ADRs were assigned to frequency categories based on incidences of similar preferred terms (PTs) for adverse events (AEs) using medical dictionary for regulatory activities (MedDRA). The frequencies are based on all reported AEs regardless of the investigator assessment of causality. The following ADRs were identified as being very common (incidence rate ≥10%): Injection site reactions (including more severe injection site related sciatica, neuralgia, neuropathic pain, and peripheral neuropathy), asthenia, joint and musculoskeletal pain (includes arthralgia, and less frequently musculoskeletal pain, back pain, myalgia and pain in extremity), nausea, hypersensitivity reactions, rash and hot flushes. Common ADRs (incidence rate ≥1% but <10%) were: headache, reduced platelet count, vomiting, diarrhoea, anorexia, and urinary tract infections.

Hepatotoxicity has been reported in patients treated with fulvestrant. Elevated liver enzymes (ALT, AST, ALP) have been reported very commonly (incidence rate ≥10%), elevated bilirubin and reduced platelet count have been reported commonly (incidence rate ≥1% but <10%), and elevated gamma-GT and hepatitis have been reporting uncommonly (incidence rate ≥0.1% and <1%) in patients treated with fulvestrant. In some cases, discontinuation of treatment resulted in improvement of transaminase and bilirubin levels. While hepatic failure was not observed in the major clinical studies with fulvestrant, post-hoc analyses of the CONFIRM study (which compared fulvestrant 500 mg with fulvestrant 250 mg) revealed the occurrence of 9 (1.2%) potential Hy's law cases that were interpreted as possibly being predictive of more severe hepatic events in the post-marketing setting.

Serious adverse events (SAEs; irrespective of causality) were typically reported at single incidences in fulvestrant 500 mg clinical trials for any given MedDRA PT. At the system organ class (SOC) level, the highest incidence of SAEs was reported in the infections and infestations SOC (incidence = 1.8%) in studies in which patients had prior anti-estrogen therapy. In the study in which patients had no prior endocrine therapy, at the SOC level, the highest incidence of SAEs was reported in the respiratory, thoracic and mediastinal disorders SOC (incidence = 4.8%).

AEs leading to permanent discontinuation of treatment (DAEs; irrespective of causality) were typically reported at single incidences in fulvestrant 500 mg clinical trials for any given MedDRA PT. At the SOC level, the highest incidence of DAEs was reported in the nervous system disorders

category (incidence = 0.5% in the studies in which patients had prior antiestrogen therapy and incidence = 1.8% in the study in which patients had no prior endocrine therapy).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Study in patients with no prior endocrine therapy

The safety of fulvestrant 500 mg versus anastrozole 1 mg was evaluated in a Phase III, randomized, double-blind, double-dummy, multicentre study (Study D699BC00001, FALCON). The data described below reflect exposure to fulvestrant in 228 out of 460 postmenopausal women with estrogen receptor-positive locally advanced or metastatic breast cancer not previously treated with endocrine therapy who received at least one dose of treatment in FALCON.

Adverse drug reactions reported in patients who received fulvestrant in the FALCON trial at an incidence of ≥5% (incidence is regardless of causality) in either treatment arm are listed in Table 1.

Table 1 Adverse Drug Reactions in the FALCON trial

Body System and Adverse Reaction	**Fulvestrant 500 mg** N=228 **(%)**	**Anastrozole 1mg** N=232 **(%)**
Vascular disorders		
Hot flush	26 (11.4)	24 (10.3)
Gastrointestinal disorders		
Nausea	24 (10.5)	24 (10.3)[a]
Diarrhea	14 (6.1)	13 (5.6)[a]
Musculoskeletal and connective tissue disorders		
Arthralgia	38 (16.7)	24 (10.3)
Myalgia	16 (7.0)	8 (3.4)
Pain in extremity	13 (5.7)	10 (4.3)
Back pain	21 (9.2)[a]	14 (6)
General disorders and administration site conditions		
Fatigue	26 (11.4)[a]	16 (6.9)

a Grade 3 or higher

Table 2 summarizes the laboratory data from both treatment arms of the FALCON study for 'elevated liver enzymes' [aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood alkaline phosphatase (ALP)] and 'elevated bilirubin'.

Table 2 Frequency data from both treatment arms of the FALCON study for laboratory abnormalities

Laboratory parameter	**Patients with any Common Terminology Criteria (CTC) grade increase from baseline**	
	Fulvestrant 500 mg n/N (%)	**Anastrozole 1mg** n/N (%)
AST increased	31/216 (14.4)	30/219 (13.7)
ALT increased	26/217 (12.0)	31/223 (13.9)
ALP increased	40/217 (18.4)	56/222 (25.2)
Bilirubin increased	8/217 (3.7)	12/222 (5.4)

n = Number of patients with an increase in CTC grade

N = Number of patients with a baseline value and at least one post-baseline value

Studies in patients with prior anti-estrogen therapy

Comparison of fulvestrant 500 mg and fulvestrant 250 mg

Safety data from the following studies were integrated for the evaluation of safety: a randomised, double-blind, parallel-group, multicentre, Phase III study (CONFIRM), a randomised, open-label, multicentre, Phase II study (NEWEST), and 2 randomised, double-blind, parallel-group, multicentre, Phase II studies (FINDER1 [Japanese patients only] and FINDER2). The data that were pooled were those available with consideration given to individual study design features such as timing of assessments. This pooled analysis of safety included data from 560 patients treated with fulvestrant 500 mg (mean exposure: 261.89 days) and 567 patients treated with fulvestrant 250 mg (mean exposure: 218.43 days). The FINDER1 and FINDER2 studies included fulvestrant 250 mg + loading dose treatment groups; the data from these patients were not included in the pooled analysis of safety as they are not relevant to the fulvestrant 500 mg vs fulvestrant 250 mg comparison.

In each study, conventional methodology was used for the assessment of the safety and tolerability of fulvestrant 500 mg, including the reporting of AEs (irrespective of causality or seriousness), treatment-related AEs as judged by the investigator, and clinical laboratory data. Any detrimental change in a patient's medical condition was considered to be an AE unless this was clearly attributable to breast cancer progression. Consequently, these safety data include AEs that would be expected in patients with advanced breast cancer and may also include the sequelae of prior or concomitant treatment. AEs were coded using MedDRA PTs.

The most common adverse events for fulvestrant 500 mg and fulvestrant 250 mg treatment arms from one Phase III and three Phase II trials are presented in Table 3.

In the pooled Phase II and Phase III safety database, the most frequently reported adverse event was injection site pain with 13.9% vs. 10.2% of patients in the fulvestrant 500 mg and 250 mg groups, respectively. This was followed by nausea, fatigue, hot flush and headache with 10.2% vs. 13.9%, 9.6% vs. 7.1%, 8.8% vs. 8.6% and 8.0% vs. 7.2%, respectively, in the 500 mg and 250 mg groups, respectively. The proportion of patients who reported at least 1 adverse event in each group was similar with 70.2% vs. 68.3 % in the fulvestrant 500 mg vs. 250 mg groups, respectively.

Table 3 Adverse events in the Fulvestrant 500 mg and Fulvestrant 250 mg treatment arms in pooled[a] data that includes CONFIRM (Phase III) and three Phase II trials (incidence ≥ 5% in either pooled group)

MedDRA preferred term[b]	Number (%) of patients, by treatment	
	Fulvestrant 500 mg	Fulvestrant 250 mg
	Pooled[a]	Pooled[a]
	500 mg (N=560)	250 mg (N=567)
Patients with any AE	**393 (70.2)**	**387 (68.3)**
Gastrointestinal Disorders		
Nausea	57 (10.2)	79 (13.9)
Vomiting	33 (5.9)	32 (5.6)
Diarrhea	30 (5.4)	24 (4.2)
General Disorders and Administration Site Conditions		
Injection site pain	78 (13.9)	58 (10.2)
Fatigue	54 (9.6)	40 (7.1)
Asthenia	29 (5.2)	31 (5.5)
Infections and Infestations		
Nasopharyngitis	24 (4.3)	33 (5.8)
Metabolism and Nutrition Disorders		
Anorexia	32 (5.7)	20 (3.5)
Musculoskeletal and Connective Tissue Disorders		
Back pain	40 (7.1)	54 (9.5)
Arthralgia	38 (6.8)	36 (6.3)
Bone pain	37 (6.6)	30 (5.3)
Pain in extremity[c]	32 (5.7)	38 (6.7)
Nervous system Disorders		
Headache	45 (8.0)	41 (7.2)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	31 (5.5)	32 (5.6)
Vascular Disorders		
Hot flush	49 (8.8)	49 (8.6)

Hypertension	24 (4.3)	29 (5.1)

[a] Pooled data: CONFIRM, NEWEST, FINDER1 and FINDER2.

[b] Patients with multiple occurrences of the same event were counted only once per event.

[c] Following data queries to the investigational sites, it was confirmed that pain in extremity was not linked to injection site pain but was a distinct and separate AE.

The organ system class is presented alphabetically and the preferred-terms are presented in order of decreasing frequency for the pooled data in the 500 mg group.

MedDRA : Medical Dictionary for Regulatory Activities.

Based on the known pharmacological and safety profile of fulvestrant, and potential safety issues for hormonal therapies, the pre-specified categories of adverse events listed in Table 4 were selected for evaluation in the CONFIRM trial.

Table 4 Number of patients experiencing pre-specified adverse events in the CONFIRM trial

Pre-specified event	**Number (%) of patients**		
	Fulvestrant 500 mg (N=361)	**Fulvestrant 250 mg (N=374)**	**p-value**
GI disturbances	73 (20.2)	76 (20.3)	1.000
Joint disorders	68 (18.8)	70 (18.7)	1.000
Injection site reactions	49 (13.6)	50 (13.4)	1.000
Hot flushes	30 (8.3)	23 (6.1)	0.318
Urinary tract infection	8 (2.2)	8 (2.1)	1.000
Ischaemic cardiovascular disorders	5 (1.4)	7 (1.9)	0.773
Thromboembolic events	3 (0.8)	6 (1.6)	0.506
Vaginitis	3 (0.8)	1 (0.3)	0.366
Weight gain	1 (0.3)	1 (0.3)	1.000
Osteoporosis	1 (0.3)	0	0.492
Endometrial dysplasia	0	0	NC

NC= Not Calculable

Comparison of Fulvestrant 250 mg and Anastrozole 1 mg

Table 5 lists adverse events reported with an incidence of ≥ 5% in the two randomised controlled trials 9238IL/0020 and 9238IL/0021, regardless of causality, during treatment or the specified safety follow-up period (defined as 8 weeks after the last injection or 30 days after ingestion of the last tablet). Both trials (9238IL/0020 and 9238IL/0021) were conducted in postmenopausal (naturally and artificially induced) women with locally advanced or metastatic breast cancer who had disease progression following anti-estrogen or progestin therapy for either advanced or early breast cancer.

Table 5 Adverse events occurring at an incidence of ≥ 5% (irrespective of causality): Combined results from Trials 9238IL/0020 and 9238IL/0021

Body System and Adverse Event[a]	**Fulvestrant 250mg (IMinjection/month) N=423 (%)**	**Anastrozole 1 mg (oral tablet/day) N=423 (%)**
Body As A Whole	68.3	67.6
Asthenia	22.7	27.0
Pain	18.9	20.3
Headache	15.4	16.8
Back Pain	14.4	13.2
Abdominal Pain	11.8	11.6
Injection Site Pain*	10.9	6.6
Pelvic Pain	9.9	9.0
Chest Pain	7.1	5.0
Flu Syndrome	7.1	6.4
Fever	6.4	6.4
Accidental Injury	4.5	5.7
Cardiovascular System	30.3	27.9
Vasodilation	17.7	17.3
Digestive System	51.5	48.0
Nausea	26.0	25.3
Vomiting	13.0	11.8
Constipation	12.5	10.6
Diarrhea	12.3	12.8
Anorexia	9.0	10.9
Hemic and Lymphatic Systems	13.7	13.5
Anemia	4.5	5.0
Metabolic and Nutritional Disorders	18.2	17.7
Peripheral Edema	9.0	10.2

Body System and Adverse Event[a]	Fulvestrant 250mg (IM injection/month) N=423 (%)	Anastrozole 1 mg (oral tablet/day) N=423 (%)
Musculoskeletal System	25.5	27.9
Bone Pain	15.8	13.7
Arthritis	2.8	6.1
Nervous System	34.3	33.8
Dizziness	6.9	6.6
Insomnia	6.9	8.5
Paresthesia	6.4	7.6
Depression	5.7	6.9
Anxiety	5.0	3.8
Respiratory System	38.5	33.6
Pharyngitis	16.1	11.6
Dyspnea	14.9	12.3
Cough increased	10.4	10.4
Skin and Appendages	22.2	23.4
Rash	7.3	8.0
Sweating	5.0	5.2
Urogenital System	18.2	14.9
Urinary tract infection	6.1	3.5

a A patient may have more then one adverse event
* All patients on Fulvestrant received injections, but only those anastrozole patients who were in the North American study received placebo injections

Post-Market Adverse Drug Reactions

Hepatic failure, hepatic necrosis, and hepatitis have been reported in patients treated with fulvestrant. In one report, a patient died due to liver failure approximately 6 months after starting treatment with fulvestrant.

DRUG INTERACTIONS

Overview

Fulvestrant does not significantly inhibit any of the major cytochrome P450 (CYP) isoenzymes *in vitro*, and results from a clinical pharmacokinetic trial in 8 healthy males involving co-administration of fulvestrant (36 mg intramuscularly) with midazolam (7.5 mg p.o.) also suggest that therapeutic doses of fulvestrant will have no inhibitory effects on CYP3A4. In addition, although fulvestrant can be metabolised by CYP3A4 *in vitro*, a clinical study in 8 healthy males with rifampicin (600 mg p.o.), an inducer of CYP3A4, showed no change in the pharmacokinetics of a 10 mg IV dose of fulvestrant as a result of the induction of CYP3A4. Results from a clinical study in 18 healthy subjects (17 male, 1 female) with ketoconazole (400 mg daily), a potent inhibitor of CYP3A4, also indicated that there is no clinically relevant change in the pharmacokinetics of an 8 mg IV dose of fulvestrant. Dosage adjustment is not necessary in patients co-prescribed CYP3A4 inhibitors or inducers.

Drug-Drug Interactions

There are no known drug-drug interactions requiring dose adjustment.

Drug-Food Interactions

Interactions with particular foods have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Due to the structural similarity of fulvestrant and estradiol, fulvestrant can interfere with estradiol measurement by immunoassays, resulting in falsely elevated levels of estradiol.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Adult Females: The recommended dose regimen of Fulvestrant Injection is 500 mg to be administered intramuscularly as two 5 mL (250 mg/5 mL) injections, one in each buttock (gluteal area) (see **Administration**). The recommended dosing schedule is as follows:
Fulvestrant Injection 500 mg dose to be administered on days 0, 14, 28 and then every 28 days thereafter.

Patients with hepatic insufficiency: No dose adjustments are recommended for patients with mild or moderate (Child Pugh Category A and B) hepatic impairment. However, as the clearance of fulvestrant may be decreased in patients with hepatic impairment, these patients should be monitored for side effects when treated with fulvestrant (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).
The use of fulvestrant has not been evaluated in patients or pharmacokinetic study women with severe (Child-Pugh Category C) hepatic impairment; therefore, it is not recommended for use in these patients.

Patients with renal insufficiency: No dose adjustments are recommended for patients with a creatinine clearance greater than 30 mL/min. Safety and efficacy have not been evaluated in patients with creatinine clearance less than 30 mL/min.

Elderly: No dose adjustment is required for elderly patients.

Children: Not recommended for use in children or adolescents, as safety and efficacy have not been established in this age group.

Administration

Instructions for use, handling and disposal

Caution should be taken if Fulvestrant Injection is injected at the dorsogluteal site due to the proximity of the underlying sciatic nerve and large blood vessels. It is recommended that the injection be administered slowly. Administer the injection according to the local guidelines for performing large volume intramuscular injections.

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

The proper method of administration of Fulvestrant Injection for intramuscular use is described in the following instructions.

For the 2 x 5 mL syringe package, the contents of both syringes must be injected to receive the 500 mg recommended dose.

For each syringe:

1. Remove syringe barrel from tray and ensure it is not damaged.

2. Inspect product prior to administration and discard if there are any visible particles or discolouration.

3. Peel open the safety needle (SafetyGlide™) outer packaging.

4. Hold the syringe upright on the ribbed part (C). With the other hand, take hold of the cap (A) and carefully tilt back and forth until the cap disconnects and can be pulled off, do not twist (Figure 1 and 2).

5. Pull the cap (A) off in a straight upward direction. To maintain sterility, do not touch the syringe tip (Luer-Lok) (B) (Figure 2).

Figure 1

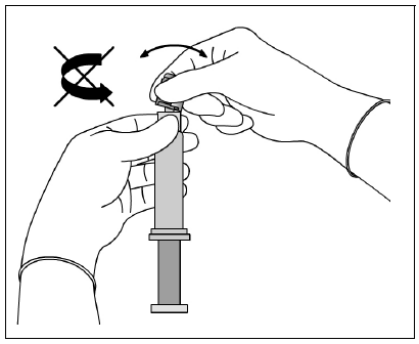
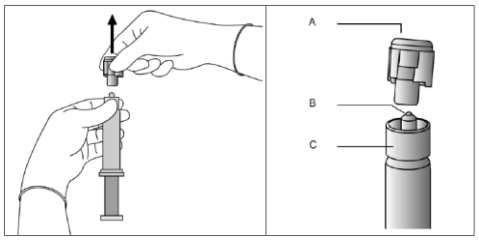


Figure 2



6. Attach the safety needle to the syringe tip (Luer-Lok) and twist until firmly seated (Figure 3). Check that the needle is locked to the Luer connector before moving or tilting the syringe out of the vertical plane to avoid spillage.

7. Pull shield straight off needle to avoid damaging needle point (keep needle shield on if transporting).

8. Expel excess gas from syringe (a small gas bubble may remain).

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

10. After injection, immediately activate the lever arm to deploy the needle shielding by applying a single-finger stroke to the activation assisted lever arm to push the lever arm completely forward. Listen for a click. Visually confirm that the needle shielding has completely covered the needle (Figure 5). NOTE: Activate away from self and others.

11. Discard empty syringe into sharps collector.

12. Repeat steps 1-11 in the other buttock with the second syringe.

SafetyGlide™ instructions are from Becton Dickinson

BD SafetyGlide™ is a trademark of Becton Dickinson and Company. Reorder number 305917.

Figure 3

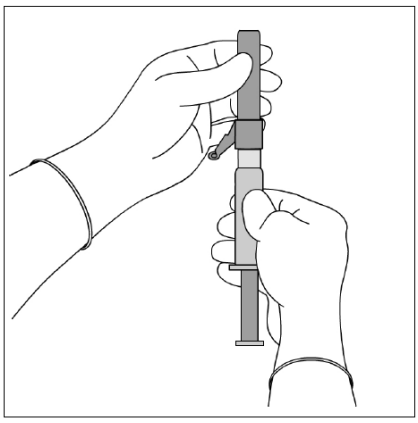


Figure 4

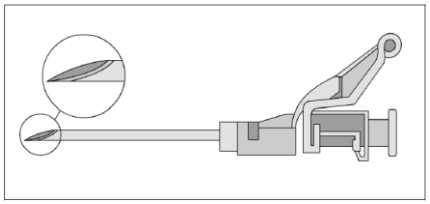
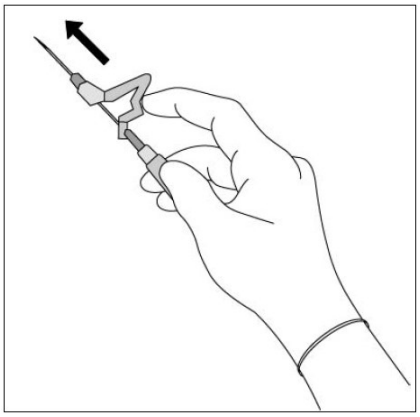


Figure 5



OVERDOSAGE

For management of suspected drug overdose, contact your regional Poison Control Centre.

There are isolated reports of overdose with fulvestrant in humans. If overdose occurs, this should be managed symptomatically. Animal studies have shown no adverse effects with intramuscular doses of greater than 400-fold of the clinical dose. Further animal studies, in which fulvestrant was dosed either monthly or twice monthly and achieved plasma levels several-fold higher than those seen in humans, showed no effects other than those related directly or indirectly to anti-estrogen activity.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Fulvestrant is an estrogen receptor (ER) antagonist that has a mode of action leading to downregulation of ER protein. Fulvestrant is a nonagonist ER antagonist that blocks the trophic actions of estrogens without itself having any partial agonist (estrogen-like) activity. Fulvestrant binds to estrogen receptors in a competitive manner with an affinity comparable to that of estradiol.

Fulvestrant is a reversible inhibitor of the growth of estrogen-sensitive human breast cancer cells *in vitro*. Fulvestrant inhibits the growth of estrogen-sensitive human breast cancer xenografts in nude mice, prevents the establishment of tumours from xenografts of human breast cancer cells, and suppresses the growth of breast tumours. Furthermore, fulvestrant inhibits the growth of tamoxifen-resistant breast cancer cells *in vitro* and of tamoxifen resistant breast tumours *in vivo*. Fulvestrant resistant breast tumours may also be cross-resistant to tamoxifen.

Pharmacodynamics

A clinical trial in postmenopausal women with primary breast cancer has shown that a single 250 mg dose of fulvestrant significantly downregulates ER expression in ER positive tumours, when compared to placebo. This same study also showed for fulvestrant a significant decrease in progesterone receptor (PgR) expression compared to placebo after 15 - 22 days of treatment. These data are consistent with fulvestrant having no agonist activity.

A trial in healthy postmenopausal volunteers showed that, compared to placebo, pre-treatment with 250 mg fulvestrant resulted in significantly reduced stimulation of the postmenopausal endometrium in volunteers treated with 20 mcg per day ethinyl estradiol. Mean endometrial thickness after treatment with 250 mg fulvestrant was 4.2 mm, and with placebo it was 11.22 mm.

In postmenopausal women, the absence of changes in plasma concentrations of FSH and LH in response to fulvestrant treatment (250 mg monthly) suggests no peripheral steroidal effects. The reduction in levels of sex hormone-binding globulin indicates a lack of agonist properties.

Pharmacokinetics

Following intravenous or intramuscular administration, fulvestrant is rapidly cleared at a rate approximating the hepatic blood flow (nominally 10.5 mL plasma/min/kg). Fulvestrant long-acting intramuscular injection maintains plasma fulvestrant concentrations within a range of up to 3-fold difference between peak and trough concentrations over a period of at least 28±3 days after injection. Administration of Fulvestrant Injection 500 mg achieves exposure levels at or close to steady state within the 1st month of dosing (see Table 6).

Results from single-dose studies of fulvestrant are predictive of multiple-dose pharmacokinetics.

Table 6 **Summary of fulvestrant pharmacokinetic parameters [gMean (CV%)] in postmenopausal advanced breast cancer patients afterintramuscular administration of the fulvestrant 500 mg dosing regimen**

		C_{max} (ng/mL)	C_{min} (ng/mL)	AUC (ng.hr/mL)
Fulvestrant 500 mg	Single dose*	25.1(35.3%)	16.3(25.9%)	11400 (33.4%)
	Multiple dose steady state**	28.0(27.9%)	12.2(21.7%)	13100(23.4%)

* Month 1of the dosing regimen (ie, Day 0, 14 and 28)
** Month 3

Absorption: Fulvestrant is not administered orally.

Distribution: Fulvestrant is subject to extensive and rapid distribution; the apparent volume of distribution at steady state is large (approximately 3 to 5 L/kg), which suggests that the compound distribution is largely extravascular. Fulvestrant is highly (99%) bound to plasma proteins. VLDL, LDL, and HDL lipoprotein fractions appear to be the major binding components. The role of sex hormone-binding globulin, if any, could not be determined. No studies were conducted on drug-drug competitive protein binding interactions, as most reported interactions of this type involved binding to albumin and α-1-acid-glycoproteins.

Metabolism: Biotransformation and disposition of fulvestrant in humans have been determined following intramuscular and intravenous administration of ^{14}C-labelled fulvestrant. Metabolism of fulvestrant appears to involve combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids, including oxidation, aromatic hydroxylation, and conjugation with glucuronic acid and/or sulphate at the 2-, 3-, and 17-positions of the steroid nucleus, and oxidation of the side chain sulphoxide. The metabolism of fulvestrant in humans yields a similar profile of metabolites to that found in other species. Identified 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 P_{450} isoenzyme involved in the oxidation of fulvestrant. However, the relative contribution of P_{450} and non-P_{450} routes *in vivo* is unknown.

Excretion: Fulvestrant is rapidly cleared by the hepatobiliary route with the overall rate of elimination being determined by the mode of administration, i.e., with monthly administration of Fulvestrant long acting intramuscular formulation, exposure, and hence elimination, is primarily determined by the rate of release from the injection site. Excretion is primarily via the feces (approximately 90%). Renal elimination of drug-related material is negligible (less than 1%).

Special Populations and Conditions

Geriatrics: No difference in the fulvestrant pharmacokinetic profile was detected with regard to age (range 33 to 89 years).

Gender: Following administration of a single intravenous dose, there were no pharmacokinetic differences between men and either premenopausal or postmenopausal women. Similarly, there were no apparent differences between men and postmenopausal women after intramuscular administration.

Race: In the advanced breast cancer treatment trials, the potential for pharmacokinetic differences due to race have been evaluated in 294 women including 87.4% Caucasian, 7.8% Black, and 4.4% Hispanic. No discernible differences in fulvestrant plasma pharmacokinetics were observed among these groups. In a separate trial, pharmacokinetic data from postmenopausal Japanese women living in Japan were comparable to those obtained in non-Japanese patients.

Hepatic Insufficiency: Fulvestrant is metabolized primarily in the liver.

The pharmacokinetics of fulvestrant has been evaluated in a single-dose clinical trial conducted in 21 women (7 women with Child-Pugh Category A and 7 with Category B hepatic impairment due to cirrhosis, 7 healthy women), using a high dose (100 mg) of a shorter duration intramuscular injection formulation. There was a 1.3 and 2.2-fold reduction in mean clearance in women with Child-Pugh Category A and B hepatic impairment, respectively, compared to healthy women. Women with mild hepatic impairment (Child-Pugh Category A) had comparable mean AUC to those with normal hepatic function, while women with moderate hepatic impairment (Child-Pugh Category B) had an increase of approximately 70% in average AUC compared to patients with normal hepatic function. Child-Pugh Category C women were not evaluated; it is expected that clearance would be further reduced in this group of women.

Modelled intramuscular mean steady state plasma concentrations of fulvestrant in women with Child-Pugh Category A and B hepatic impairment fall within the upper 95% confidence limit of the mean steady state concentrations expected for patients with normal hepatic function given the intramuscular formulation. Given the known safety profile of fulvestrant, no dose adjustment is considered to be necessary in patients with Child-Pugh Category A or B hepatic impairment, although they should be monitored for side effects. Fulvestrant is not recommended for use in patients with severe (Child-Pugh Category C) hepatic impairment.

STORAGE AND STABILITY

Store refrigerated at 2°C to 8°C. Store in original package and do not break the seal, in order to protect it from light.
Single use. Discard unused portion.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Fulvestrant Injection is a clear, colourless to yellow, viscous liquid. In addition to the active ingredient fulvestrant, each pre-filled syringe contains the following inactive ingredients: alcohol 96%, benzyl alcohol, benzyl benzoate, and refined castor oil.

Fulvestrant Injection is available in a package of two 250 mg/5 mL (50 mg/mL) pre-filled syringes. Each syringe is presented in a tray with polypropylene plunger rod and a 21G x 1 ½ inches (0.8mm x 40mm) safety needle (SafetyGlide™) for connection to the barrel.

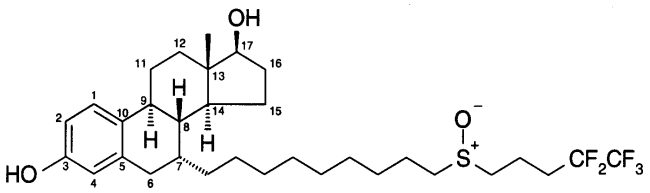
As with all parenteral drug products, syringes should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Drug Substance

Common Name:	fulvestrant
Chemical Name:	7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl) nonyl]estra-1,3,5-(10)- triene-3,17β-diol
Molecular Formula and Molecular Mass:	$C_{32}H_{47}F_5O_3S$ and 606.8 g/mol
Structural Formula:	
Physiochemical Properties:	The active ingredient fulvestrant is a white crystalline solid powder. Fulvestrant injection solution for injection is a clear, colourless to yellow, viscous liquid. Fulvestrant has a very high lipophilicity and extremely low aqueous solubility. Fulvestrant is very soluble in alcohols (>200 mg/mL in benzyl alcohol and ethanol) and glycols (70 mg/mL in propylene glycol) and poorly soluble in fixed oils with the exception of castor oil in which solubility is 13 mg/mL.

CLINICAL TRIALS

There were no clinical trials conducted with fulvestrant in the premenopausal population. Some women of premenopausal age with advanced breast cancer were entered in fulvestrant clinical studies provided they met the protocol definition for postmenopausal status.

In patients with no prior endocrine therapy, efficacy of fulvestrant 500 mg was established in FALCON (Study D699BC00001).

In patients with prior anti-estrogen therapy, efficacy of fulvestrant was established for fulvestrant 250 mg compared to anastrozole in clinical trials 9238IL/0020 and 9238IL/0021.
The efficacy of fulvestrant 500 mg versus fulvestrant 250 mg was established in CONFIRM (Study D6997C00002).

Study in patients with no prior endocrine therapy

A Phase III, randomized, double-blind, double-dummy, multicentre study (Study D699BC00001, FALCON) evaluated fulvestrant 500 mg versus anastrozole 1 mg in postmenopausal women with ER-positive and/or PgR-positive, HER2-negative locally advanced or metastatic breast cancer

who had not previously been treated with any endocrine therapy. A total of 462 patients were randomized 1:1 to receive fulvestrant 500 mg as intramuscular injection on Days 0, 14, 28 and every 28 (±3) days thereafter or daily administration of anastrozole 1 mg orally.

Randomization was stratified by disease setting (locally advanced or metastatic), use of prior chemotherapy for advanced disease, and presence or absence of 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 Tumors). Key secondary efficacy endpoints included overall survival (OS) and objective response rate (ORR).

The demographic characteristics of patients in the FALCON intention to treat (ITT) analysis set at study entry are summarized in Table 7.

Table 7 Demographic characteristics: FALCON ITT analysis set

Demographic characteristic		**Number (%) of subjects**	
		Fulvestrant 500 mg (N=230)	**Anastrozole 1 mg (N=232)**
Sex n (%)	Female	230 (100)	232 (100)
	Total	230 (100)	232 (100)
Age (years)	Mean (SDev)	63.8 (9.86)	63.3 (10.38)
	Median	64.0	62.0
	Range	38 - 87	36 - 90
Age group (years) n (%)	<50	14 (6.1)	14 (6.0)
	≥50 to <65	108 (47.0)	127 (54.7)
	≥65	108 (47.0)	91 (39.2)
Race n (%)	Caucasian	175 (76.1)	174 (75.0)
	Asian	36 (15.7)	34 (14.7)
	Other	14 (6.1)	15 (6.5)
	Black or African American	4 (1.7)	4 (1.7)
	American Indian or Alaska Native	1 (0.4)	5 (2.2)

Note: Ethnicity reported here differs from the geographical groups used for the subgroup analyses.
ITT: Intention to treat; N: Number of patients; Max: Maximum; Min: Minimum; SDev: Standard deviation

The baseline disease characteristics and relevant medical history of patients in the FALCON ITT analysis set are shown in Table 8.

Table 8 Baseline disease characteristics and medical history: FALCON ITT analysis set

Baseline characteristic	Number (%) of patients	
	Fulvestrant 500 mg (N=230)	Anastrozole 1 mg (N=232)
Tumour biomarker characteristics		
ER and PgR receptor status		
ER+, PgR+	175 (76.1)	179 (77.2)
ER+, PgR-	44 (19.1)	43 (18.5)
ER-, PgR+	1 (0.4)	3 (1.3)
ER-, PgR-	0	0
Unknown	10 (4.3)	7 (3.0)
HER2 receptor status		
Positive	0	1 (0.4)
Negative	230 (100)	231 (99.6)
Tumour grade		
Well differentiated (G1)	15 (6.5)	21 (9.1)
Moderately differentiated (G2)	108 (47.0)	111 (47.8)
Poorly differentiated (G3)	46 (20.0)	27 (11.6)
Undifferentiated (G4)	1 (0.4)	4 (1.7)
Unassessable (GX)	59 (25.7)	68 (29.3)
Unknown	1 (0.4)	1 (0.4)
Baseline disease characteristics		
Time from diagnosis to randomisation		
≤2 months	102 (44.3)	99 (42.7)
>2 months to ≤1 year	58 (25.2)	66 (28.4)
>1 year	70 (30.4)	67 (28.9)
Disease stage		
Locally advanced only	28 (12.2)	32 (13.8)
Metastatic	202 (87.8)	200 (86.2)
Sites of metastases		
Bone/locomotor	144 (62.6)	127 (54.7)
Lymph nodes	125 (54.3)	107 (46.1)
Respiratory	97 (42.2)	88 (37.9)
Liver (including gall bladder)	42 (18.3)	43 (18.5)
Measurable disease		
Yes	193 (83.9)	196 (84.5)
No	37 (16.1)	36 (15.5)
Disease sites at baseline		
Visceral disease[a]	135 (58.7)	119 (51.3)
Bone/Locomotor only	24 (10.4)	24 (10.3)

Baseline characteristic	Number (%) of patients	
	Fulvestrant 500 mg (N=230)	Anastrozole 1 mg (N=232)
Skin/Soft tissue only	8 (3.5)	6 (2.6)
Breast only	3 (1.3)	2 (0.9)
WHO Performance Status		
0: Normal activity	117 (50.9)	115 (49.6)
1: Restricted activity	106 (46.1)	105 (45.3)
2: In bed ≤50% of the time	7 (3.0)	12 (5.2)
3: In bed >50% of the time	0	0
4: 100% bed ridden	0	0
Previous treatment modalities[b]		
Chemotherapy	79 (34.3)	81 (34.9)
Advanced disease[c]	36 (15.7)	43 (18.5)
Adjuvant	35 (15.2)	27 (11.6)
Neo-adjuvant	11 (4.8)	16 (6.9)
Recurrent disease	0	0
Radiotherapy	53 (23.0)	50 (21.6)
Immunotherapy	0	0
Hormonal therapy	2 (0.9)	1 (0.4)
Other systemic anticancer treatment	0	0

ITT: Intention to treat; N: Number of patients; ER: Estrogen receptor; PgR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; WHO: World Health Organisation

a. Visceral disease includes subjects with disease site at baseline of adrenal, bladder, central nervous system, oesophagus, liver, lung, peritoneum, pleura, renal, small bowel, stomach, pancreas, thyroid, colon, rectal, ovary, biliary tract, ascites, pericardial effusion, spleen or pleural effusion.

b. Previous to study treatment, as deemed by the sponsor to be relevant to the interpretation of the results

c. Includes first line, second line, third line, metastatic and palliative chemotherapies

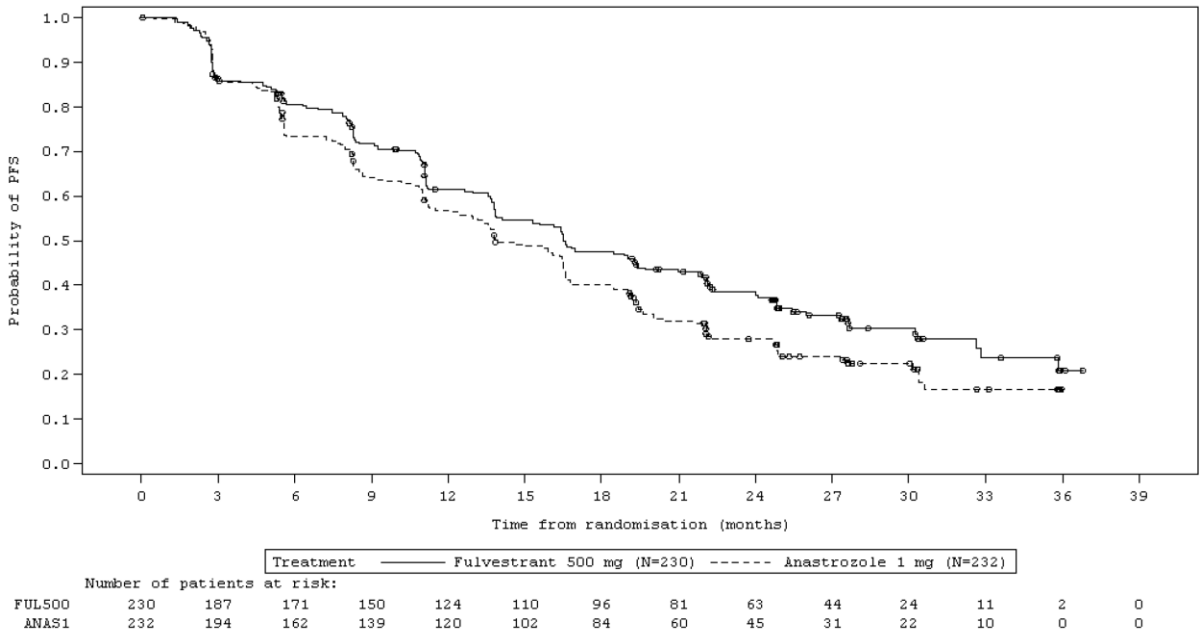
The primary efficacy results of the FALCON study are presented in Table 9 and Figure 6.

Consistent results were observed across the majority of pre-specified patient subgroups. Among those subgroups which did not show consistent PFS results with the primary analysis, the hazard ratio for the pre-specified subgroup of patients with visceral metastasis (n=254) was 0.993 (95% CI: 0.740, 1.331) with a median PFS of 13.8 months for the fulvestrant arm compared to 15.9 months for the anastrozole arm. For the pre-specified subgroup of patients with disease limited to non-visceral metastasis (n=208), the hazard ratio was 0.592 (95% CI: 0.419, 0.837) with a median PFS of 22.3 months for the fulvestrant arm compared to 13.8 months for the anastrozole arm.

Table 9 FALCON (Study D699BC00001) - Summary of efficacy results of the primary and key secondary efficacy endpoints (Investigator Assessment, ITT Population)

Variable	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)

Figure 6 Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment, ITT Population) ─ FALCON Study



In an interim analysis of OS, there was no statistically significant difference between the treatment arms (HR 0.875; 95% CI 0.629 to 1.217; 2-sided p=0.4277). The ORR (for patients with measurable disease) was similar in the fulvestrant (46.1%) and anastrozole (44.9%) treatment arms (Odds Ratio 1.074; 95% CI: 0.716, 1.614; 2-sided p=0.7290).

Studies in patients with prior anti-estrogen therapy

Comparison of Fulvestrant 250 mg and Anastrozole 1 mg

Fulvestrant was studied in two randomised, controlled clinical trials [a North American study (9238IL/0021), and a predominantly European study (9238IL/0020)] in postmenopausal (naturally and artificially induced) women with locally advanced or metastatic breast cancer who had disease progression following endocrine therapy (excluding aromatase inhibitors) for either advanced or

early breast cancer. The majority of patients in these trials were ER+ and/or PgR+. Patients who had ER-/PgR- or unknown disease were required to have shown a prior response to endocrine therapy to be eligible to participate in the trials.

A total of 851 patients between the ages of 33 and 89 years old were randomised to receive trial treatment. These patients received either fulvestrant 250 mg intramuscularly once a month, or anastrozole 1 mg orally once a day. In addition, a total of 163 patients were randomised to a 125 mg per month dose, but an interim analysis showed a very low response rate and this low dose group was discontinued.

Table 10 provides the demographics and baseline characteristics of the postmenopausal women randomised in Trials 9238IL/0020 and 9238IL/0021.

Table 10 Trials 9238IL/0020 and 9238IL/0021 - Demographics and baseline characteristics

	North American Trial 9238IL/0021		European Trial 9238IL/0020	
Parameter	**Fulvestrant 250 mg**	**Anastrozole 1 mg**	**Fulvestrant 250 mg**	**Anastrozole 1 mg**
No. of Participants	206	194	222	229
Mean Age (yrs)	63	62	63	64
Age Range (yrs)	33 - 89	36 - 94	35 - 86	33 - 89
Hormone Receptor Status # (%)				
ER and/or PgR positive	179 (87%)	169 (87%)	163 (73%)	183 (80%)
ER/PgR negative[a]	14 (7%)	10 (5%)	8 (4%)	9 (4%)
ER and PgR unknown	13 (6%)	15 (8%)	51 (23%)	37 (16%)
Prior treatment				
Adjuvant endocrine[b]	122 (59%)	116 (60%)	121 (55%)	119 (52%)
Endocrine therapy for advanced disease	110 (53%)	97 (50%)	126 (57%)	129 (56%)
Cytotoxic chemotherapy	129 (63%)	122 (63%)	94 (42%)	98 (43%)
Extent of metastatic or recurrent disease at baseline				
Soft Tissue only	12 (6%)	13 (7%)	11 (5%)	8 (4%)
Bone only	47 (23%)	43 (22%)	38 (17%)	40 (18%)
Visceral only	39 (19%)	45 (23%)	30 (14%)	41 (18%)
Lymph node only	15 (7%)	17 (9%)	22 (10%)	21 (9%)
Not recorded	1 (1%)	2 (1%)	0	1 (0%)
Mixed*	92 (45%)	87 (45%)	121 (55%)	118 (52%)

a ER/PgR negative is defined as ER negative and either PgR negative or PgR unknown
b Adjuvant endocrine therapy included tamoxifen for >95% of patients
* Mixed is defined as breast and/or a combination of skin, bone, liver, lung, or lymph nodes

Trial results

The primary efficacy endpoint was progression-free survival; secondary endpoints included objective response, clinical benefit, time to treatment failure, quality of life and survival. Overall, fulvestrant was shown to be at least as effective as anastrozole in terms of progression-free survival, in a non-inferiority analysis.

The efficacy results are presented in Table 11. Figures 7 and 8 show Kaplan-Meier plot of these data for Trials 9238IL/0020 and 9238IL/0021, respectively.

Table 11 Trials 9238IL/0020 and 9238IL/0021 - Efficacy Results

	North American Trial (9238IL/0021)		**Predominantly European Trial (9238IL/0020)**		**Combined Trials (9238IL/0021 & 9238IL/0020)**	
End Point	Fulvestrant 250 mg (n=206)	Anastrozole 1 mg (n=194)	Fulvestrant 250 mg (n=222)	Anastrozole 1 mg (n=229)	Fulvestrant 250 mg (n=423)	Anastrozole 1 mg (n=423)
Progression-Free Survival (PFS) Median PFS (days)	167.4	103.5	167.4	155.2	167.6	124.8
Hazard Ratio (FAS/ANA) 2-sided 95.14%	0.92 (0.74, 1.14)		0.98 (0.80, 1.21)		0.95 (0.82, 1.10)	
Objective Tumour Response Number (%) of women with CR + PR	36 (17.5)	34 (17.5)	46 (20.7)	36 (15.7)	82 (19.2)	70 (16.5)
% Difference in Tumour Response Rate (FAS/ANA) 2-sided 95.14% CI	+0.2% (-6.3, +9.3)		+4.8% (-2.2, +14.2)		+2.8% (-2.3, +9.0)	
Survival Time Died n (%) Median Survival (days)	152 (73.8%) 844	149 (76.8%) 913	167 (75.2%) 803	173 (75.5%) 736	319 (74.5%) 833	322 (76.1%) 844
Hazard Ratio 2-sided 95% CI	0.98 (0.78, 1.24)		0.97 (0.78, 1.21)		0.98 (0.84, 1.15)	

CR = Complete Response; PR = Partial Response; CI = Confidence Interval
FAS = Fulvestrant
ANA = Anastrozole

Figure 7 Kaplan Meier Probability of Progression-Free Survival (patients included: all patients randomised to fulvestrant 250 mg or anatrozole 1 mg - predominantly European Trial; 9238IL/0020)

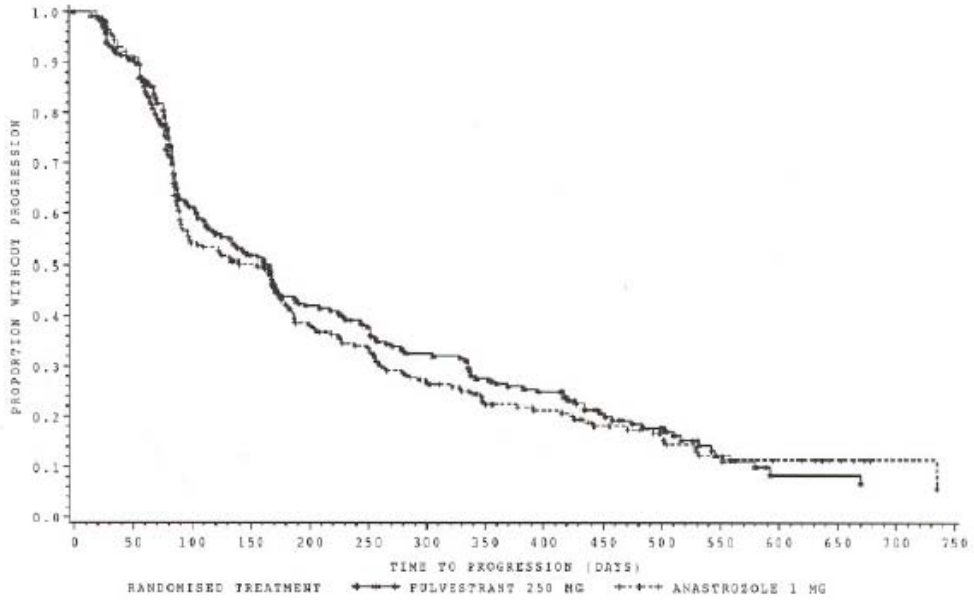
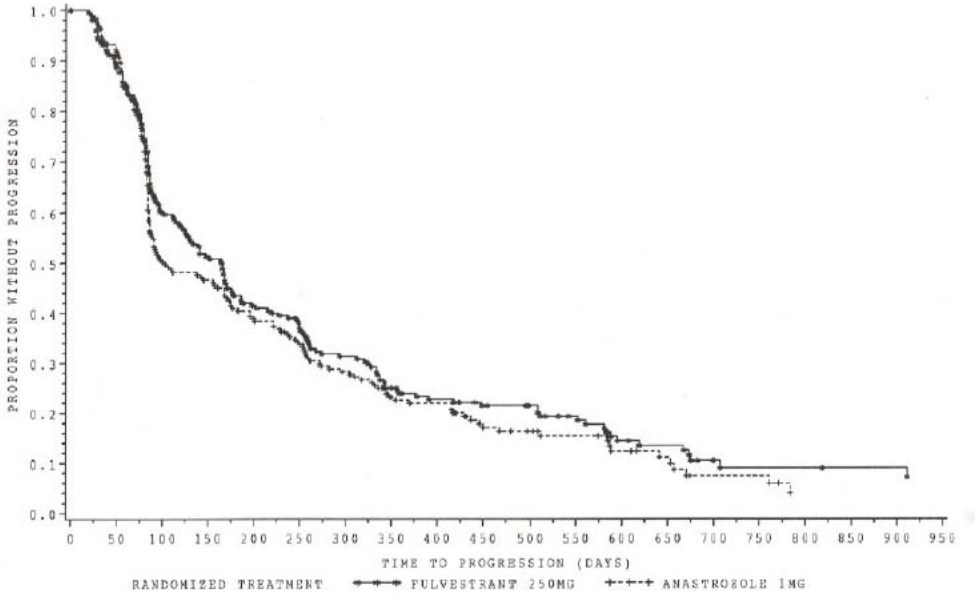


Figure 8 Kaplan Meier Probability of Progression-Free Survival (patients included: all patients randomised to fulvestrant 250 mg or anastrozole 1 mg – North American Trial; 9238IL/0021)



Comparison of Fulvestrant 500 mg and Fulvestrant 250 mg

A Phase III clinical trial (CONFIRM; Trial D6997C00002) 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. This trial compared the efficacy and safety of fulvestrant 500 mg with fulvestrant 250 mg Progression-Free Survival (PFS), defined as the time from randomisation to the time of the earliest evidence of objective disease progression or death from any cause was the primary endpoint. Objective response rate (ORR), overall survival (OS), clinical benefit rate (CBR), duration of response (DoR), and duration of clinical benefit (DoCB), were all secondary efficacy endpoints.

Fulvestrant 500 mg was administered as two 5 mL injections each containing fulvestrant 250 mg/5 mL, once in each buttock on Days 0, 14, 28 and every 28 (+/- 3) days thereafter. Fulvestrant 250 mg was administered as two 5 mL injections (one containing fulvestrant 250 mg/5 mL injection plus one placebo injection) one in each buttock on Days 0, 14 (2 placebo injections only), 28 and every 28 (+/-) days thereafter.

Table 12 provides the demographics and baseline characteristics of the postmenopausal women randomized to fulvestrant 500 mg or fulvestrant 250 mg.

Table 12 CONFIRM (Trial D6997C00002) - Demographics and baseline characteristics

	Trial D6997C00002	
Parameter	**Fulvestrant 500 mg**	**Fulvestrant 250 mg**
No. of Participants	362	374
Median Age (yrs)	61.0	61.0
Age Range (yrs)	26 - 91	23 - 87
Hormone Receptor Status # (%)		
ER+ve	362 (100.0)	374 (100.0)
PgR+ve	241 (66.6)	266 (71.1)
PgR-ve	92 (25.4)	96 (25.7)
PgR unknown	29 (8.0)	12 (3.2)
Disease Characteristics (at randomization)		
Locally advanced breast cancer only	4 (1.1)	11 (2.9)
Metastatic disease	358 (98.9)	363 (97.1)
Any visceral disease	205 (56.6)	198 (52.9)
Bone only	87 (24.0)	77 (20.6)
Measurable Disease		
No	112 (30.9)	113 (30.2)
Yes	240 (66.3)	261 (69.8)
Previous Therapy		
Adjuvant therapy[a]		
Endocrine therapy	231 (63.8)	249 (66.6)
Aromatase inhibitor	52 (14.4)	55 (14.7)
Anti-estrogen	202 (55.8)	217 (58.0)
Chemotherapy	185 (51.1)	200 (53.5)
Radiotherapy	214 (59.1)	206 (55.1)

Advanced disease therapy[a]		
Endocrine therapy	173 (47.8)	182 (48.7)
Aromatase inhibitor	101 (27.9)	108 (28.9)
Anti-estrogen	72 (19.9)	75 (20.1)
Chemotherapy	81 (22.4)	69 (18.4)
Radiotherapy	69 (19.1)	102 (27.3)
Last endocrine therapy received[b]		
Aromatase inhibitor	52 (42.0)	161 (43.0)
Anti-estrogen	210 (58.0)	213 (57.0)

a Categories are not mutually exclusive.
b Patients who had received 2 previous endocrine therapies could be eligible provided that they have started the advanced endocrine treatment at least 12 months after the completion of adjuvant endocrine treatment.

Trial results

In CONFIRM, the primary efficacy endpoint of Progression-Free Survival (PFS) was significantly longer for fulvestrant 500 mg than for fulvestrant 250 mg, demonstrating a 20% (Hazard ratio [95% CI] = 0.80 [0.68 to 0.94]; p=0.006) reduction in the risk of disease progression and a median increase of 1 month in the time to progression.

Table 13 shows the PFS data for all randomised patients to the fulvestrant 500 mg or fulvestrant 250 mg treatment arms in CONFIRM (Trial D6997C00002); Figure 9 shows a Kaplan-Meier plot of these data. At the time of the primary analysis, the minimum duration of follow-up was 18 months.

Table 13 CONFIRM (Trial D6997C00002) - Summary of Progression-Free Survival: Includes all randomised patients to either Fulvestrant 500 mg or Fulvestrant 250 mg

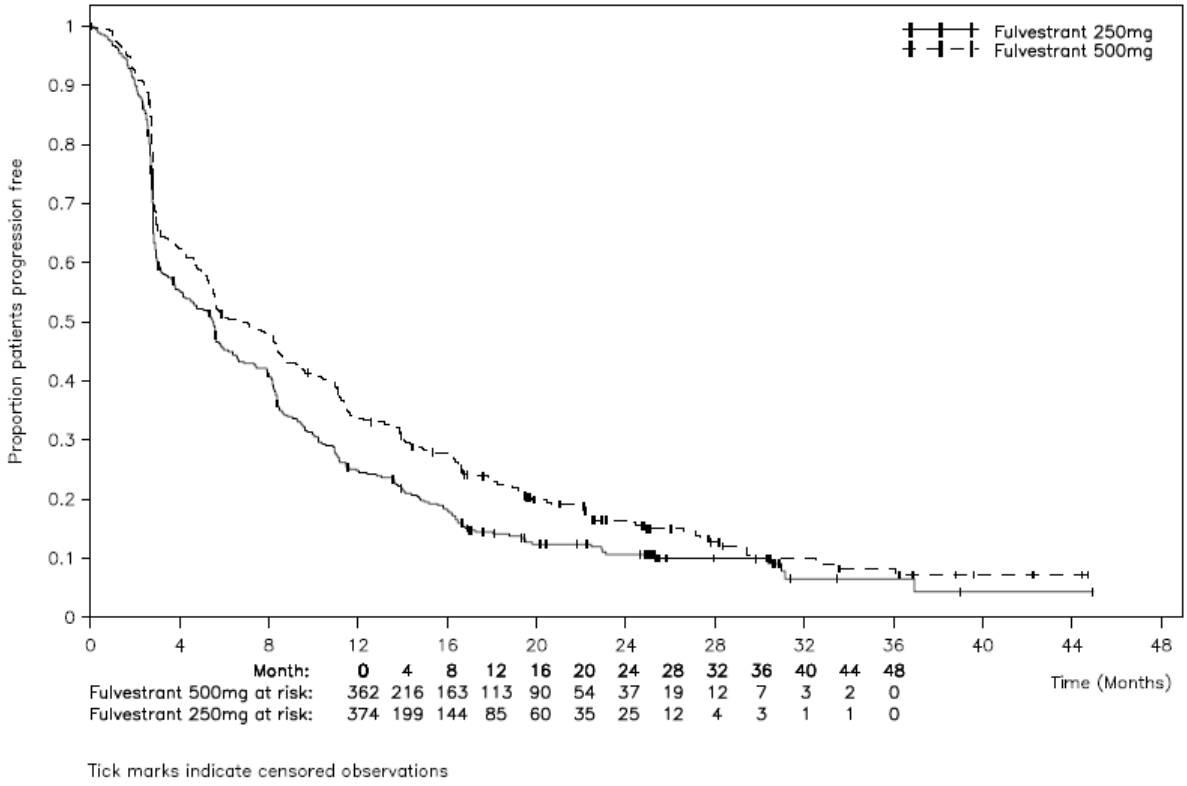
	Fulvestrant 500 mg N=362	**Fulvestrant 250 mg N=374**
Number progressed (%)	297 (82.0)	321 (85.8)
Median (months)	6.5	5.5
Progression-Free Survival (months): 25% quartile	2.8	2.7
Progression-Free Survival (months): 75% quartile	16.6	11.9
Percentage of patients progression free at:		
6 months	51%	45%
12 months	34%	25%
18 months	23%	14%
24 months	16%	11%
Hazard ratio (95% CI)	0.80 (0.68–0.94)	
p-value	0.006	

Progression-Free Survival is the time between randomisation and the earliest of progression or death from any cause.

A hazard ratio <1 indicates FASLODEX 500 mg is associated with a longer time to disease progression than FASLODEX 250 mg

A hazard ratio >1 indicates FASLODEX 500 mg is associated with a shorter time to disease progression than FASLODEX 250 mg

Figure 9 CONFIRM (Trial D6997C00002) - Kaplan-Meier plot of Progression-Free Survival: Includes all patients randomised to either Fulvestrant 500 mg or Fulvestrant 250 mg in CONFIRM trial



The primary analysis of PFS is supported by the Cox proportional hazards regression analysis, adjusted for treatment and 6 specified covariates (hazard ratio=0.78 [95% CI 0.67 to 0.92]; p=0.003).

Subgroup analyses of the primary endpoint (PFS) were performed for 6 pre-defined covariates: receptor status, visceral involvement, response to last endocrine therapy, measurable disease, age and last endocrine therapy received prior to fulvestrant. The observed treatment effect in favour of fulvestrant 500 mg over fulvestrant 250 mg was consistent across all subgroups. A global interaction test on PFS was conducted to determine whether there was any heterogeneity in the

treatment effect across the 6 predefined covariates; no evidence of heterogeneity was found (p=0.801). Nevertheless, it is important to mention that the study was not powered to detect interaction between the investigated covariates and treatment activity.

Table 14 shows the efficacy results for the secondary outcome variables at the time of the primary analysis (minimum follow-up duration of 18 months).

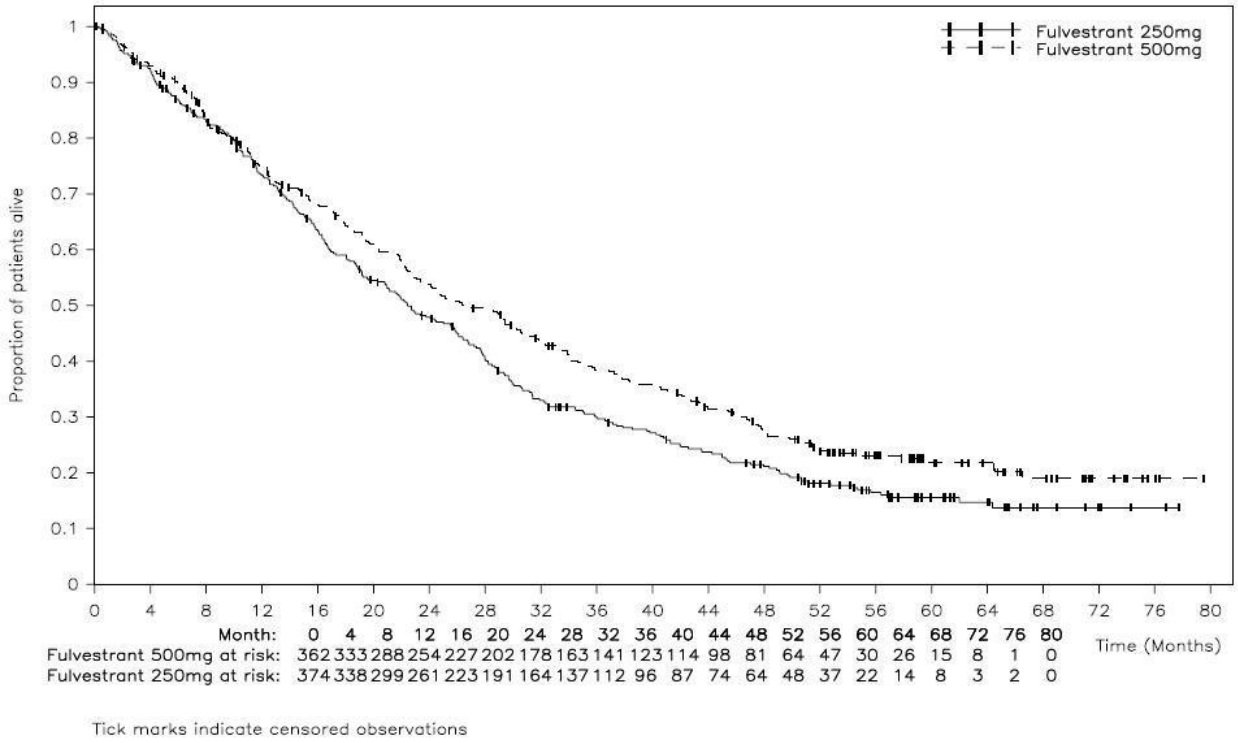
Table 14 CONFIRM (Trial D6997C00002) Summary of efficacy results for the secondary endpoints

Variable	FASLODEX 500mg	FASLODEX 250mg	
Objective response rate	13.8%	14.6%	Odds ratio=0.94 (95% CI -0.57–1.55); p=0.795
Clinical benefit rate	45.6%	39.6%	Odds ratio=1.28 (95% CI 0.95–1.71); p=0.100
Duration of response (median)	19.4 months	16.4 months	Ratio of expected duration of response=0.894 (95% CI 0.479–1.667); p=0.724
Duration of clinical benefit(median)	16.6 months	13.9 months	Ratio of expected duration of clinical benefit=1.357 (95% CI 1.067–1.726); p=0.013
Overall survival (median)	25.1 months	22. 8 months	Hazard ratio=0.84 (95% CI 0.69–1.030); p=0.091

* measured from randomisation to progression
A hazard ratio <1 indicates fulvestrant 500 mg is associated with a longer time to disease progression than fulvestrant 250 mg
A hazard ratio >1 indicates fulvestrant 500 mg is associated with a shorter time to disease progression than fulvestrant 250 mg
An odds ratio >1 favours fulvestrant 500 mg whereas an odds ratio of <1 favours fulvestrant 250 mg

After a minimum follow-up duration of 50 months, an updated overall survival (OS) analysis demonstrated a non-statistically significant improvement in median OS of 4.1 months (Hazard ratio [95% CI] = 0.81 [0.69-0.96]; p=0.016 [nominal p-value as no adjustment was made for multiplicity]). Figure 10 shows a Kaplan-Meier plot of the updated overall survival data after a minimum follow-up duration of 50 months.

Figure 10 CONFIRM (Trial D6997C00002) - Kaplan-Meier plot of Overall Survival (minimum follow-up duration of 50 months): Includes all patients randomised to either Fulvestrant 500 mg or Fulvestrant 250 mg in CONFIRM trial



Effects on breast cancer tissue *in vivo*

Clinical trials in postmenopausal women with primary breast cancer have shown that fulvestrant significantly downregulates estrogen receptor (ER) expression in ER positive tumours in a dose dependent manner. There was also a significant decrease in progesterone receptor (PR) expression, an estrogen-regulated protein consistent with the preclinical data demonstrating that fulvestrant lacks intrinsic estrogen agonist activity. These changes in ER and PR expression were accompanied by reductions in expression of Ki67, a marker of tumour cell proliferation, which were also related to dose with fulvestrant 500 mg having a significantly greater effect than the 250 mg dose.

Effects on the postmenopausal endometrium

Data suggests that fulvestrant will not have a stimulatory effect on the postmenopausal endometrium. A trial in healthy postmenopausal volunteers showed that compared to placebo, pre-treatment with 250 mg fulvestrant resulted in significantly reduced stimulation of the postmenopausal endometrium in volunteers treated with 20 mcg per day ethinyl estradiol. This demonstrates an antiestrogenic effect on the postmenopausal endometrium.

Treatment for up to 16 weeks in breast cancer patients treated with either fulvestrant 500 mg or 250 mg did not result in clinically significant changes in endometrial thickness, indicating of a lack of agonist effect.

Effects on bone

Treatment for up to 16 weeks in breast cancer patients treated with either fulvestrant 500 mg or 250 mg did not result in clinically significant changes in serum bone-turnover markers. There are no long-term data on the effect of fulvestrant on bone. Due to the mode of action of fulvestrant, there is a potential risk of osteoporosis.

DETAILED PHARMACOLOGY

Pharmacodynamics

Fulvestrant is a potent inhibitor of the growth of ER positive MCF-7 human breast cancer cells. In intact adult female rats, treatment with fulvestrant proved effective in blocking the trophic action of endogenous estrogens on the uterus. The potency of fulvestrant against endogenous estrogen ($ED_{50} \approx 0.1$ mg/kg/day subcutaneous) was similar to that found in the ovariectomized, estradiol-treated rat ($ED_{50} \approx 0.07$ mg/kg subcutaneous).

Changes in the cornification of the vaginal smears also indicated a similar potency of fulvestrant against estrogen effects on the vagina (partial and complete blockade at 0.1 and 0.3 mg/kg subcutaneous, respectively).

The anti-tumour activity of fulvestrant was assessed in mice bearing tumours derived from the MCF-7 human breast cancer cell line or from explants of the human breast tumour-derived solid tumour, Br10. A single subcutaneous injection of 5 mg of fulvestrant blocked completely the growth of MCF-7-derived human breast tumour xenografts in nude mice for at least four weeks. The growth of transplants of the Br10 human breast tumour was also suppressed effectively by fulvestrant. A single subcutaneous injection of 5 mg fulvestrant on the day of tumour implantation showed a substantial and sustained reduction of tumour growth, compared with controls. Ovariectomy of all the animals after 3 months demonstrated the estrogen sensitivity of the tumours.

Independent studies showed that tamoxifen-resistant MCF-7 xenografts in nude mice, which grow out after long-term treatment with tamoxifen, remain sensitive to fulvestrant treatment.

Pharmacokinetics

Fulvestrant was well absorbed and widely distributed into the tissues following intramuscular administration, and is eliminated almost entirely in bile in rats and dogs. Metabolism was qualitatively similar in rats, dogs and man. Although some metabolites possess intrinsic activity similar to the parent, they were not detectable in the plasma and were quantitatively minor metabolites (<10%). The results suggest that fulvestrant itself is responsible for the observed pharmacological activity *in vivo*. Adequate exposure to fulvestrant was achieved in the rat and dog relative to man.

In rats, fulvestrant was generally released slowly from the long-acting formulation throughout a 30-day measurement period. T_{max} was variable (between 3 hours and 11 days after dosing) and group mean AUC ($_{0\text{-}30\ days}$) increased proportional to dose. In dogs, group mean AUC($_{0\text{-}28\ days}$) was also dose proportional and the time to C_{max} (T_{max}) varied between 2 and 7 days. Monthly intramuscular injections to dogs resulted in a slight accumulation, but there was no evidence of an increase in C_{max}.

TOXICOLOGY

Acute Toxicity

The acute toxicity of fulvestrant is low. In rodents, the median lethal dose was greater than 70 mg/kg following intramuscular administration (more than 400-times the clinical dose), greater than 50 mg/kg following intravenous administration, and greater than 2000 mg/kg following oral administration.

Repeat Dose Toxicity

Fulvestrant was well tolerated in all animal species in which it was tested. In multiple, intramuscular dose toxicity studies in rats and dogs, the antiestrogenic 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. There was no evidence of other systemic toxicity in rats dosed up to 10 mg/rat/15 days for 6 months or in dogs dosed up to 40 mg/kg/28 days for 12 months.

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, but these occurred in animals exposed to far higher levels of fulvestrant than those recorded in patients (C_{max} >15 times) and are, therefore, considered to be of no significance for human safety at the clinical dose.

Carcinogenicity and Mutagenicity

A two-year carcinogenesis study was conducted in female and male rats, at intramuscular doses of 15 mg/kg/30 days, 10 mg/rat/30 days and 10 mg/rat/15 days. These doses correspond to approximately 0.9-, 1.5-, and 3-fold (in females) and 0.8-, 0.8-, and 2.0-fold (in males) the systemic exposure [AUC_{0-30} days] achieved in women receiving the recommended dose of 500 mg/month. An increased incidence of benign ovarian granulosa cell tumours and testicular Leydig cell tumours was evident, in females dosed at 10 mg/rat/15 days and males dosed at 15 mg/rat/30 days, respectively. In a two-year mouse oncogenicity study, oral dosing was associated with an increased incidence of sex cord stromal tumours (both benign and malignant) in the ovary at doses of 150 and 500 mg/kg/day. The no-observed-effect level (NOEL) for these findings was 10 mg/rat/30 days in the rats and 20 mg/kg/day in the mice, respectively. Induction of such tumours is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an anti-estrogen. Therefore these findings are not considered to be relevant to use of fulvestrant in postmenopausal women.

Fulvestrant was not mutagenetic or clastogenic in multiple *in vitro* tests with and without the addition of a mammalian liver metabolic activation factor (bacterial mutation assay in strains of *Salmonella typhimurium* and *Escherchia coli*, *in vitro* cytogenetics study in human lymphocytes, mammalian cell mutation assay in mouse lymphoma cells and *in vivo* micronucleus test in rat).

Reproduction and Teratology

In a variety of reproductive toxicology studies, rats were dosed intramuscularly with 0.001 -2 mg/kg/day (0.007 - 13 mg/m^2, based on body surface area) and rabbits were dosed with 0.01 - 0.25 mg/kg/day (0.1 - 2.5 mg/m^2, based on body surface area). In comparison, the human clinical dose,

500 mg/month, equates to approximately 13.4 mg/m^2. On a mg/m^2 basis, these animal studies showed that at doses similar to, or lower than the clinical dose of fulvestrant, there were effects upon reproduction as well as embryo/fetal development consistent with its antiestrogenic activity. Fulvestrant has been shown to cross the placenta following single intramuscular doses of 1.0 mg/kg in rats and 0.26 mg/kg in rabbits.

In rats, fulvestrant caused a reversible reduction in female fertility and in embryonic survival at dose levels of 0.01 mg/kg/day and above (approximately 0.6% of the human dose, based on body surface area), dystocia, and an increased incidence of fetal abnormalities, including tarsal flexure. Dosing with 0.1 mg /kg/day and above (approximately 6% of the human dose on a body surface area basis) resulted in evidence of delayed fetal development including an increased incidence in non-ossification of the odontoid and the ventral tubercle of the first cervical vertebra. An increased incidence in tarsal flexure was seen with 2.0 mg/kg/day (equivalent to the human dose on a mg/m^2 basis) when fulvestrant was administered during organogenesis. Other major fetal anomalies occurring at 2 mg/kg/day included the following: edema, gastroschisis, shortened digits, flexion of the hindpaw, and shortening of the upper and lower jaw.

Rabbits given fulvestrant (≥ 1mg/kg/day, equivalent to the human dose on a mg/m^2 basis), during the period of major organogenesis, failed to maintain pregnancy. In addition, at 0.25 mg/kg/day (one-quarter the human dose on a mg/m^2 basis), increases in placental weight and post-implantation loss were seen, but no fetal abnormalities were observed. There was, however, an increased incidence of fetal variations, common in rabbits (backwards displacement of the pelvic girdle, and 27 pre-sacral vertebrae) at 0.25 mg/kg/day (one- quarter the human dose on a mg/m^2 basis), when dosed during the period of organogenesis.

The potential effects of fulvestrant on the fertility of male animals were not studied, however, in a 6-month toxicology study, male rats treated with intramuscular doses of 15 mg/kg/30 days, 10 mg/rat/30 days or 10 mg/rat/15 days, fulvestrant showed a loss of spermatozoa from the seminiferous tubules, seminiferous tubular atrophy, and degenerative changes in the epididymides. Changes in the testes and epididymides had not recovered 20 weeks after cessation of dosing. These fulvestrant doses correspond to approximately 1.3-, 1.2-, and 3.5-fold the systemic exposure [AUC_{0-30} days] achieved in women receiving the recommended dose of 500 mg/month.

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

Pr FULVESTRANT INJECTION
fulvestrant injection
50 mg/mL

This leaflet is part III of a three-part "Product Monograph" published when Fulvestrant Injection was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Fulvestrant Injection. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Fulvestrant Injection is used to treat breast cancer in postmenopausal women.

What it does:
In hormone sensitive breast cancer, estrogen (female sex hormone) promotes tumour growth. By stopping some of the actions of estrogen, Fulvestrant Injection reduces the amount that is in the body, which has an effect in reducing breast cancer tumour growth.

When it should not be used:
- If you are allergic to this drug or any of its ingredients (see important non-medicinal ingredients).
- If you are pregnant or breast-feeding.

What the medicinal ingredient is:
fulvestrant

What the important non-medicinal ingredients are:
Alcohol 96%, benzyl alcohol, benzyl benzoate and refined castor oil.

What dosage forms it comes in:
Sterile injection solution in pre-filled syringes.
Each pre-filled syringe has 250 mg of fulvestrant.

WARNINGS AND PRECAUTIONS

Fulvestrant Injection is not expected to affect your ability to drive or use machines. However, some patients may occasionally feel tired and/or weak. If this happens to you, do not drive or operate machines and ask your doctor for advice. Fulvestrant Injection should not be given to children or men.

BEFORE you use Fulvestrant Injection talk to your doctor or pharmacist if:
- If you have any problems with your liver or kidneys.
- If you have been told you have a low blood platelet count, problems with bleeding or if you use medicine to prevent blood clots (e.g. anticoagulants).
- If you have a personal or family history of osteoporosis (thinning of the bone), or have low bone density, or have a recent history of fracture.
- If you can become pregnant, you should use effective contraception while you are being treated with Fulvestrant Injection and for 2 years after your last dose.

DURING treatment with Fulvestrant Injection, contact your doctor promptly if the following happens to you, as you may need further examination or treatment:

- allergic reactions, including swelling of the face, lips, tongue and/or throat, hives/welts and/or difficulty with swallowing. Such reactions may happen immediately, or several days after injection.

INTERACTIONS WITH THIS MEDICATION

Interactions with other drugs and Fulvestrant have not been established. Before using Fulvestrant Injection talk to your doctor or pharmacist if you are taking, or have recently taken any other medicines, even those you have bought without prescription.

PROPER USE OF THIS MEDICATION

Fulvestrant Injection is to be given as an injection into the muscle (intramuscular) of the buttock. Your healthcare provider will administer this medicine.

Usual dose:
500 mg as two 250 mg/5 mL injections, one in each buttock on days 0, 14 and 28 and then every 28 days thereafter.

Overdose:

If you think you have taken too much Fulvestrant Injection, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss your scheduled dose, call your doctor immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Fulvestrant Injection can have side effects. Tell your doctor as soon as possible if any of the following side effects bothers you or continues.

During Fulvestrant Injection treatment, you may also have the following side effects which are seen when a blood test is taken:

- increased level of liver enzymes (very common)
- increased level of bilirubin (common)
- increased level of an enzyme called Gamma-glutamyl transferase produced in the liver (uncommon)

SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/ effect	Talk with your healthcare professional		Stop taking drug and get immediate help
	Only if severe	In all cases	
Very Common			
Injection site reactions, such as pain and/or inflammation		√	
Weakness		√	
Fatigue		√	
Nausea		√	
Joint, muscle and back pain		√	
Hot flushes		√	
Skin rash		√	

SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/ effect	Talk with your healthcare professional		Stop taking drug and get immediate help
	Only if severe	In all cases	
Allergic reactions, including swelling of the face, lips, tongue and/or throat, hives/welts and/or difficulty with swallowing. Such reactions may happen immediately, or several days after injection.		√	
Common			
Feelings of numbness, tingling or weakness in your legs following a Fulvestrant Injection.		√	
Headache		√	
Pain in extremity		√	
Symptoms from the stomach or the bowels, such as vomiting, diarrhea or loss of appetite		√	
Urinary tract infections		√	
Lower level of platelets (symptoms may include bruising, reddish-purple spots and unusual bleeding)		√	
Uncommon			

SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom/ effect	**Talk with your healthcare professional**		**Stop taking drug and get immediate help**
	Only if severe	**In all cases**	
Inflammation of the liver. Symptoms may include a general feeling of being unwell, with or without jaundice (yellowing of the skin and eyes), liver pain or liver swelling.		√	

If you notice any other side effects, please tell your doctor or pharmacist as soon as possible.
This is not a complete list of side effects. For any unexpected effects while taking Fulvestrant Injection, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.

Fulvestrant Injection must be kept in the refrigerator (2°C-8°C). The pre-filled syringe will normally be stored for you by your doctor or the hospital. The staff is responsible for the correct storage, use and disposal of Fulvestrant Injection.

Keep the Fulvestrant Injection syringe in its original pack and do not break the seal, in order to protect it from light. The Fulvestrant Injection pre-filled syringe should not be used after the expiry date on the pack.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about Fulvestrant Injection:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by calling the sponsor Accord Healthcare Inc. at 1-866-296-0354.

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