SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Faslodex 250 mg solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to yellow, viscous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Faslodex is indicated 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.

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.

Special populations
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, Faslodex 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 Faslodex 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
Faslodex 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 Faslodex at the dorsogluteal site due to the proximity of the underlying sciatic nerve.

For detailed instructions for administration, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Faslodex 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, Faslodex 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 Faslodex (see section 4.8). This should be taken into consideration when prescribing Faslodex to patients at risk.

Injection site related events including sciatica, neuralgia, neuropathic pain, and peripheral neuropathy have been reported with Faslodex injection. Caution should be taken while administering Faslodex 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.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Patients of child-bearing potential should be advised to use effective contraception while on treatment.

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

Breast-feeding
Breast-feeding must be discontinued during treatment with Faslodex. 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 Faslodex on fertility in humans has not been studied.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

This section provides information based on all adverse reactions from clinical studies, post-marketing studies or spontaneous reports. The most frequently reported adverse reactions are injection site reactions, asthenia, nausea, and increased hepatic enzymes (ALT, AST, ALP).

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

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

Table 1 Adverse Drug Reactions

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]
Metabolism and nutrition disorders	Common	Anorexia[a]
Nervous system disorders	Common	Headache
Vascular disorders	Very common	Hot flushes[e]
	Common	Venous thromboembolism[a]
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting, diarrhoea
Hepatobiliary disorders	Very common	Elevated hepatic enzymes (ALT, AST, ALP)[a]

	Common	Elevated bilirubin[a]
	Uncommon	Hepatic failure[c, f], hepatitis[f], elevated gamma-GT[f]
Skin and subcutaneous tissue disorders	Very common	Rash[e]
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], leukorrhea[f]
General disorders and administration site conditions	Very common	Asthenia[a], injection site reactions[b]
	Common	Neuropathy peripheral[e], sciatica[e]
	Uncommon	Injection site haemorrhage[f], injection site haematoma[f], neuralgia[c,f]

[a] Includes adverse drug reactions for which the exact contribution of Faslodex 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 Faslodex 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy, Antiestrogens, ATC code: L02BA03

Mechanism of action and pharmacodynamic effects

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

Clinical efficacy and safety in advanced breast cancer

A Phase 3 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 antiestrogen 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 Faslodex 500 mg (n=362) with Faslodex 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 2.

Table 2 Summary of results of the primary efficacy endpoint (PFS) and key secondary efficacy endpoints in the CONFIRM study

Variable	Type of estimate; treatment comparison	Faslodex 500 mg (N=362)	Faslodex 250 mg (N=374)	Comparison between groups (Faslodex 500 mg/Faslodex 250 mg)		
				Hazard ratio	95% CI	p-value
PFS	**K-M median in months; hazard ratio**					
All Patients		6.5	5.5	0.80	0.68, 0.94	0.006
-AE subgroup (n=423)		8.6	5.8	0.76	0.62, 0.94	0.013
-AI subgroup (n=313)[a]		5.4	4.1	0.85	0.67, 1.08	0.195
OS[b]	**K-M median in months; hazard ratio**					
All Patients		26.4	22.3	0.81	0.69, 0.96	0.016[c]
-AE subgroup (n=423)		30.6	23.9	0.79	0.63, 0.99	0.038[c]
-AI subgroup (n=313)[a]		24.1	20.8	0.86	0.67, 1.11	0.241[c]
Variable	**Type of estimate; treatment comparison**	**Faslodex 500 mg (N=362)**	**Faslodex 250 mg (N=374)**	**Comparison between groups (Faslodex 500 mg/Faslodex 250 mg)**		
				Absolute difference in %	**95% CI**	
ORR[d]	**% of patients with OR; absolute difference in %**					
All Patients		13.8	14.6	-0.8	-5.8, 6.3	
-AE subgroup (n=296)		18.1	19.1	-1.0	-8.2, 9.3	
-AI subgroup (n=205)[a]		7.3	8.3	-1.0	-5.5, 9.8	

CBR[e]	**% of patients with CB; absolute difference in %**				
All Patients		45.6	39.6	6.0	-1.1, 13.3
-AE subgroup (n=423)		52.4	45.1	7.3	-2.2, 16.6
-AI subgroup (n=313)[a]		36.2	32.3	3.9	-6.1, 15.2

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

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

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

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

[e] Patients with a best objective response of complete response, partial response or stable disease ≥24 weeks.
PFS:Progression-free survival; ORR:Objective response rate; OR:Objective response; CBR:Clinical benefit rate; CB:Clinical benefit; OS:Overall survival; K-M:Kaplan-Meier; CI:Confidence interval; AI:Aromatase inhibitor; AE:Antiestrogen.

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

Randomisation was stratified by disease setting (locally advanced or metastatic), prior chemotherapy for advanced disease, and measurable disease.

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

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

Consistent results were observed across the majority of pre-specified patient subgroups. For the subgroup of patients with disease limited to non-visceral metastasis (n=208), the HR was 0.592 (95% CI: 0.419, 0.837) for the Faslodex arm compared to the anastrozole arm. For the subgroup of patients with visceral metastasis (n=254), the HR was 0.993 (95% CI: 0.740, 1.331) for the Faslodex arm compared to the anastrozole arm. The efficacy results of the FALCON study are presented in Table 3 and Figure 1.

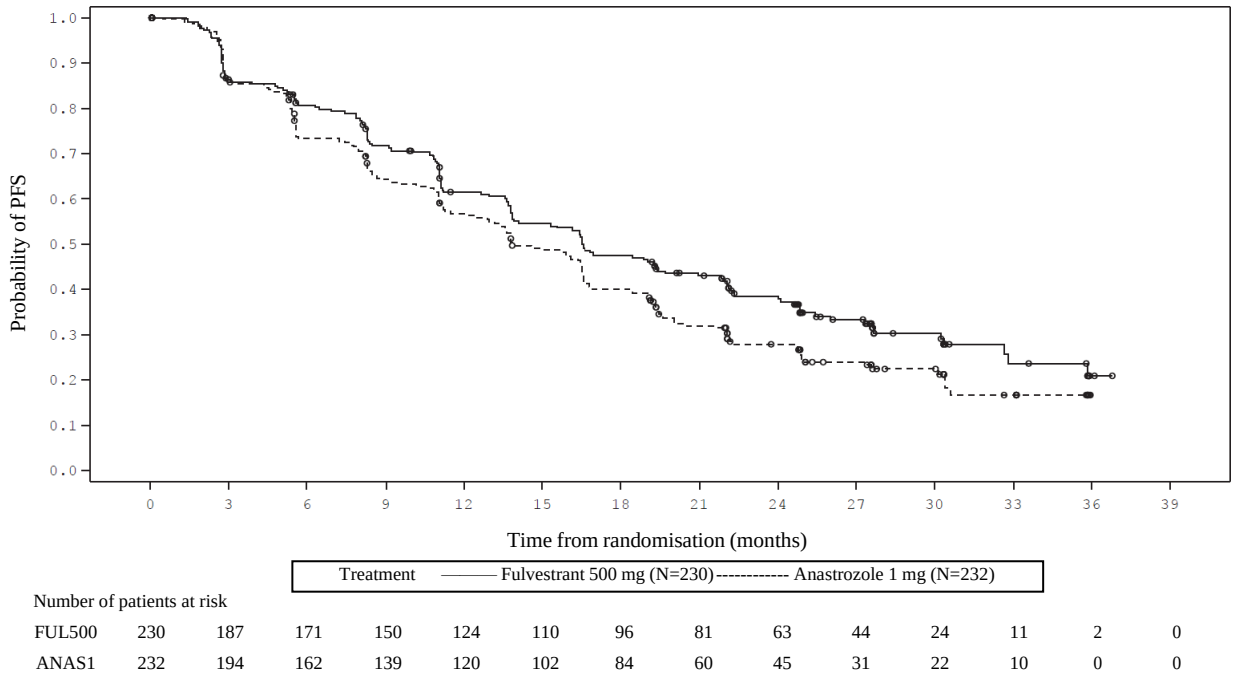
Table 3 Summary of results of the primary efficacy endpoint (PFS) and key secondary efficacy endpoints (Investigator Assessment, Intent-To-Treat Population) – FALCON study

	Faslodex 500 mg (N=230)	**Anastrozole 1 mg (N=232)**
Progression-Free Survival		
Number of PFS Events (%)	**143 (62.2%)**	**166 (71.6%)**
PFS Hazard Ratio (95% CI) and p-value	**HR 0.797 (0.637 - 0.999) p = 0.0486**	
PFS Median [months (95% CI)]	**16.6 (13.8, 21.0)**	**13.8 (12.0, 16.6)**

Number of OS Events*	**67 (29.1%)**	**75 (32.3%)**
OS Hazard Ratio (95% CI) and p-value	**HR 0.875 (0.629 – 1.217) p = 0.4277**	
ORR**	**89 (46.1%)**	**88 (44.9%)**
ORR Odds Ratio (95% CI) and p-value	**OR 1.074 (0.716 – 1.614) p = 0.7290**	
Median DoR (months)	**20.0**	**13.2**
CBR	**180 (78.3%)**	**172 (74.1%)**
CBR Odds Ratio (95% CI) and p-value	**OR 1.253 (0.815 – 1.932) p = 0.3045**	

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

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



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 Faslodex 250 mg versus the daily administration of 1 mg anastrozole (aromatase inhibitor). Overall, Faslodex 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 Faslodex progressed, compared with 85% of patients who received anastrozole. Combined analysis of both studies showed the hazard ratio of Faslodex 250 mg to anastrozole for progression-free survival was 0.95 (95% CI 0.82 to 1.10). The objective response rate for Faslodex 250 mg was 19.2% compared with 16.5% for anastrozole. The median time to death was 27.4 months for patients treated with Faslodex and 27.6 months for patients treated with anastrozole. The hazard ratio of Faslodex 250 mg to anastrozole for time to death was 1.01 (95% CI 0.86 to 1.19).

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 μg per day ethinylestradiol showed that pretreatment with Faslodex 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 Faslodex 500 mg or Faslodex 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 Faslodex 500 mg or Faslodex 250 mg did not result in clinically significant changes in serum bone-turnover markers.

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

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

5.2 Pharmacokinetic properties

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

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

Biotransformation

The metabolism of fulvestrant has not been fully evaluated, but involves combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids. Identified metabolites (includes 17-ketone, sulphone, 3-sulphate, 3- and 17-glucuronide metabolites) are either less active or exhibit similar activity to fulvestrant in antiestrogen 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 3 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 women with hepatic impairment compared to healthy subjects. In patients administered Faslodex, 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.

Faslodex 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 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. 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 antiestrogenic 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 Faslodex) 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 antiestrogens in cycling animals. Therefore these findings are not considered to be relevant to the use of fulvestrant in postmenopausal women with advanced breast cancer.

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

4 years

6.4 Special precautions for storage

Store and transport in a refrigerator (2°C - 8°C).

Temperature excursions outside 2°C - 8°C should be limited. This includes avoiding storage at temperatures exceeding 30°C, and not exceeding a 28 day period where the average storage temperature for the product is below 25°C (but above 2°C - 8°C). After temperature excursions, the product should be returned immediately to the recommended storage conditions (store and transport in a refrigerator 2°C - 8°C). Temperature excursions have a cumulative effect on the product quality and the 28 day time period must not be exceeded over the duration of the 4-year shelf life of Faslodex (see section 6.3). Exposure to temperatures below 2°C will not damage the product providing it is not stored below – 20°C.

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

6.5 Nature and contents of container

BD SafetyGlide is a trademark of Becton Dickinson and Company and is CE-marked: CE 0050.

The pre-filled syringe presentation consists of:

One clear type 1 glass pre-filled syringe with polystyrene plunger rod, fitted with a tamper-evident closure, containing 5 ml Faslodex solution for injection.
A safety needle (BD SafetyGlide™) for connection to the barrel is also provided.
Or
Two clear type 1 glass pre-filled syringes with polystyrene plunger rod, fitted with a tamper-evident closure, each containing 5 ml Faslodex solution for injection. Safety needles (BD SafetyGlide™) for connection to each barrel are also provided.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for administration

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

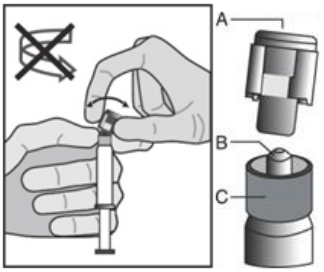
NOTE: Due to the proximity of the underlying sciatic nerve, caution should be taken if administering Faslodex at the dorsogluteal injection site (see section 4.4).

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.

For each of the two syringes:

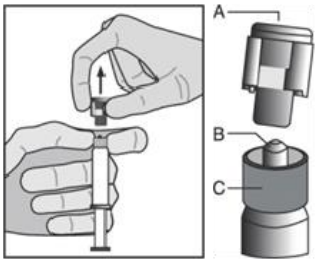
- Remove glass syringe barrel from tray and check that it is not damaged.
- Peel open the safety needle (SafetyGlide™) outer packaging.
- Parenteral solutions must be inspected visually for particulate matter and discolouration prior to administration.
- Hold the syringe upright on the ribbed part (C). With the other hand, take hold of the cap (A) and carefully tilt back and forth until the cap disconnects and can be pulled off, do not twist (see Figure 1).

Figure 1



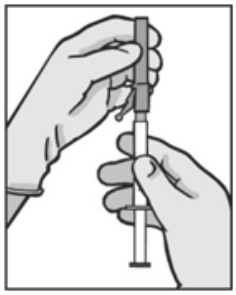
- Remove the cap (A) in a straight upward direction. To maintain sterility do not touch the syringe tip (B) (see Figure 2).

Figure 2



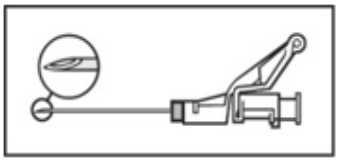
- Attach the safety needle to the Luer-Lok and twist until firmly seated (see Figure 3).
- Check that the needle is locked to the Luer connector before moving out of the vertical plane.
- Pull shield straight off needle to avoid damaging needle point.
- Transport filled syringe to point of administration.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

Figure 3



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

Figure 4



- After injection, immediately apply a single-finger stroke to the activation assisted lever arm to activate the shielding mechanism (see Figure 5).
  NOTE: Activate away from self and others. Listen for click and visually confirm needle tip is fully covered.

Figure 5

Disposal
Pre-filled syringes are for single use **only**.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited
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8. MARKETING AUTHORISATION NUMBER(S)

04585/06869/N
MR/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: Aug 12, 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu