AUSTRALIAN PRODUCT INFORMATION
FULVESTRANT EVER PHARMA®
(fulvestrant)

1 NAME OF THE MEDICINE
fulvestrant.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
FULVESTRANT EVER PHARMA contains 250 mg/5 mL fulvestrant drug substance.

Fulvestrant is a white powder with low aqueous solubility. Only 1 morphological form is known to exist. Fulvestrant is highly lipophilic and does not ionise at physiological pH.

Excipients with known effects: benzyl benzoate and ethanol. For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM
FULVESTRANT EVER PHARMA 250 mg/5 mL solution for injection is a pre-filled syringe with clear, colourless to yellow, viscous liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
FULVESTRANT EVER PHARMA is indicated for the treatment of postmenopausal women with

- hormone-receptor (HR) positive, human epidermal growth factor receptor 2(HER2) negative, locally advanced or metastatic breast cancer who have not been previously treated with endocrine therapy.
- HR positive, locally advanced or metastatic breast cancer who have progressive disease following prior endocrine (anti-oestrogen or aromatase inhibitor) therapy.

4.2 Dose and method of administration
In the absence of incompatibility studies, FULVESTRANT EVER PHARMA must not be mixed with other drugs. FULVESTRANT EVER PHARMA is not recommended for use in men.

Product is for single use in one patient only. Discard any residue.

Adult females (including the elderly)
The recommended dose (500 mg) is to be administered intramuscularly as two 5 mL injections, one in each buttock (gluteal area), at intervals of 1 month.

An additional 500 mg dose is to be given 2 weeks after the initial dose.

It is recommended that the injection be administered slowly (1-2 minutes/injection).

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

Special patient populations

Patients with hepatic insufficiency
No dose adjustments are recommended for patients with mild hepatic impairment. Safety and efficacy have not been further evaluated in patients with moderate to severe hepatic impairment (see Section 4.4 Special warnings and precautions for use).

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 further evaluated in patients with creatinine clearance less than 30 mL/min (see Section 4.4 Special warnings and precautions for use).

Use in the elderly
No dose adjustment is required for elderly patients.

Paediatric use
Not recommended for use in children or adolescents as safety and effectiveness have not been established in this age group.

4.3 Contraindications
FULVESTRANT EVER PHARMA is contraindicated in patients with a known hypersensitivity to the drug substance or to any of the excipients.

FULVESTRANT EVER PHARMA is contraindicated in pregnancy.

4.4 Special warnings and precautions for use
Use in hepatic impairment
Fulvestrant is metabolised primarily in the liver. In clinical trials in patients with advanced breast cancer, in which FULVESTRANT EVER PHARMA has been administered to patients with mild hepatic impairment (alanine aminotransferase concentration greater than the upper limit of the normal reference range [ULN] but less than twice the ULN). There was no clear relationship between fulvestrant clearance and hepatic impairment. The safety profile in patients with mild hepatic impairment was similar to that seen in patients with no hepatic impairment. Caution should be used with FULVESTRANT EVER PHARMA in patients with moderate to severe hepatic impairment, as clearance may be reduced.

Use in renal impairment
Caution should be used before treating patients with creatinine clearance less than 30 mL/min. See Section 5.2 Pharmacokinetic properties.

Coagulation disorders
Caution should be used before treating patients with bleeding diatheses or thrombocytopenia or patients on anticoagulants due to the route of administration.

Injection site related events
Injection site related events including sciatica, neuralgia, neuropathic pain, and peripheral neuropathy have been reported with FULVESTRANT EVER PHARMA injection. Caution should be taken while administering FULVESTRANT EVER PHARMA at the dorsogluteal injection site due to the proximity of the underlying sciatic nerve (see Sections 4.2 Dosage and method of administration and 4.8 Adverse effects (Undesirable effects)).

Use in the elderly
See Section 4.2 Dose and method of administration.

Paediatric use
See Section 4.2 Dose and method of administration.

Effects on laboratory tests
Interference with oestradiol assay
Due to the structural similarity of fulvestrant and oestradiol, fulvestrant may interfere with antibody based oestradiol assays and may result in falsely increased levels of oestradiol.

4.5 Interactions with other medicines and other forms of interactions
Fulvestrant does not significantly inhibit any of the major cytochrome P450 (CYP) isoenzymes in vitro, and results from a clinical pharmacokinetic trial involving co-administration of fulvestrant with midazolam 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 with rifampicin showed no change in fulvestrant clearance as a result of the induction of CYP3A4. Dosage adjustment is not necessary in patients co-prescribed CYP3A4 inhibitors or inducers.

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

4.6 Fertility, pregnancy and lactation
Effects on fertility
Fulvestrant affected oestrus cycling in rats causing a reduction in female fertility at doses as low as 0.01 mg/kg/day, considerably lower than the clinical dose on a body surface area basis. Embryonic survival was also reduced. These effects are consistent with the antioestrogenic activity of fulvestrant. These effects were largely reversible in rats after a 1-month withdrawal period from the drug. FULVESTRANT EVER PHARMA is not proposed for use in males, but loss of spermatozoa from the seminiferous tubules, seminiferous tubular atrophy and degenerative changes in the epidiymides were observed in a 6-month study in rats given fulvestrant by the intramuscular route.

Use in pregnancy – Category D
FULVESTRANT EVER PHARMA is proposed for use in postmenopausal women only. FULVESTRANT EVER PHARMA may cause foetal harm when administered to a pregnant woman. If FULVESTRANT EVER PHARMA is used during pregnancy or if the patient becomes pregnant while receiving this drug, the patient should be informed of the potential hazard to the foetus or potential risk for loss of the pregnancy. If FULVESTRANT EVER PHARMA is used in patients of childbearing potential, patients should use effective contraception during treatment with FULVESTRANT EVER PHARMA and for 2 years after the last dose. In rats, fulvestrant caused a reversible reduction in embryonic survival at intramuscular doses as low as 0.01 mg/kg/day, considerably lower than the clinical dose calculated on a body surface area basis. Fulvestrant also caused dystocia and an increased occurrence of foetal abnormalities in rats, including tarsal flexure, at an intramuscular dose of 2 mg/kg/day, corresponding to approximately twice the clinical dose calculated on a body surface area basis. Rabbits given intramuscular fulvestrant at ≥1 mg/kg/day (corresponding to approximately twice the clinical dose calculated on a body surface area) failed to maintain pregnancy, while at doses of 0.25 mg/kg/day, there were small increases in post-implantation loss, placental weight and incidences of two foetal variations.

Use in lactation
Studies in rats have shown that fulvestrant levels in rat milk are significantly higher than those in rat plasma. The potential risk for nursing infants is unknown. Therefore, breastfeeding should be avoided in women receiving FULVESTRANT EVER PHARMA.

4.7 Effects on ability to drive and use machines
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.

4.8 Adverse effects (Undesirable effects)

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

Table 1 Summary of Adverse Drug Reactions (ADR) seen in clinical trials for fulvestrant 500 mg

Frequency descriptor	System Order Class	ADR
Very common (≥ 10%)	General disorders and administration site conditions	Injection site reactions[c], asthenia
	Hepatobiliary disorders	Elevated liver enzymes (ALT, AST, ALP)[a]
	Gastrointestinal disorders	Nausea
	Immune system disorders	Hypersensitivity reactions[e]
	Musculoskeletal and connective tissue disorders	Joint and musculoskeletal pain[d]
	Skin and subcutaneous tissue disorders	Rash[e]
	Vascular disorders	Hot flushes[e]
Common (≥1 - <10%)	Nervous system disorders	Headache
	Hepatobiliary disorders	Elevated bilirubin[a]
	Blood and lymphatic system	Reduced platelet count[e]
	Gastrointestinal disorders	Vomiting, diarrhoea
	Metabolism and nutrition disorders	Anorexia
	Infections and infestations	Urinary tract infections
Uncommon (≥0.1% and <1%)	Hepatobiliary disorders	Hepatic failure[b,f], hepatitis[f], elevated gamma-GT[f]

[a] Based on any CTC grade change from baseline.

[b] The event was not observed in major clinical studies (CONFIRM, FINDER1, FINDER2, 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 560is the number of patients in the major clinical studies), which equates to a frequency category of 'uncommon'

[c] Including more severe injection site related sciatica, neuralgia, neuropathic pain, and peripheral neuropathy.

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

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

[f] ADR was not observed in FALCON.

In the combined studies (CONFIRM, NEWEST, FIRST, FINDER1 and FINDER2) the adverse effect profile of the 500 mg dose was comparable to that seen with the 250 mg dose but more cases of osteoporosis (4 vs 0), vaginitis (3 vs 1) and pruritus (23 vs 8) were reported with the higher dose.

Table 2 lists adverse experiences reported with an incidence of 5% or greater, regardless of assessed causality, from the two controlled clinical trials comparing the administration of fulvestrant 250 mg intramuscularly once a month with anastrozole 1 mg orally once a day.

Body system and adverse event[a]	**Fulvestrant 250 mg N=423 (%)**	**Anastrozole 1 mg N=423 (%)**
Body as a whole	69.7	68.8
Asthenia	24.6	27.9
Pain	20.3	22.5
Headache	16.5	17.7
Back pain	16.1	15.4
Abdominal pain	12.8	13.2
Injection site pain*	11.3	6.9
Pelvic Pain	11.1	9.9
Chest pain	7.6	5.7
Flu syndrome	8.5	7.1
Fever	7.6	6.9
Accidental injury	5.4	6.1
Cardiovascular system	31.9	32.2
Vasodilatation	18.4	18.7
Hypertension	5.4	5.7
Digestive system	53.9	49.9
Nausea	28.1	27.0
Vomiting	15.1	12.3
Constipation	13.9	11.8
Diarrhoea	13.9	13.9
Anorexia	9.9	11.3
Haemic and lymphatic Systems	15.6	14.7
Anaemia	5.9	5.7
Metabolic and Nutritional disorders	21.5	21.0
Peripheral oedema	10.9	11.3
Musculoskeletal system	29.1	31.7
Bone pain	18.0	15.4
Myalgia	4.5	5.0
Arthritis	3.8	6.9
Nervous system	38.1	37.1
Dizziness	8.0	7.3
Insomnia	8.3	9.9
Paresthaesia	7.1	8.7
Depression	6.4	7.8
Anxiety	5.4	4.7
Respiratory system	40.7	35.7

Body system and adverse event[a]	Fulvestrant 250 mg N=423 (%)	Anastrozole 1 mg N=423 (%)
Pharyngitis	17.3	12.5
Dyspnoea	16.1	13.5
Cough increased	12.3	12.1
Sinusitis	3.8	5.2
Skin and appendages	24.1	25.8
Rash	9.2	9.0
Sweating	5.2	5.7
Urogenital system	20.1	18.9
Urinary tract infection	6.9	4.7

[a] A patient may have more than one adverse event.

*All patients on fulvestrant received injections, but only those anastrozole patients who were in the North American study received placebo injections.

Fulvestrant has been commonly associated with elevation of liver enzymes, the vast majority <2 x ULN (frequency >1 - <10%).

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose
There are isolated reports of overdose with fulvestrant in humans. If overdose occurs, this should be managed symptomatically. The acute toxicity of fulvestrant in laboratory animal species is low. Animal studies suggested that no effects, other than those related directly or indirectly to antioestrogenic activity, were evident with higher doses of fulvestrant. 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).

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Mechanism of action
Fulvestrant is an antioestrogen that binds to oestrogen receptors in a competitive manner, with a high affinity comparable to that of oestradiol, and downregulates the oestrogen receptor. Fulvestrant completely inhibited the uterotrophic action of exogenous oestradiol, but showed no agonistic effects in uterotrophic assays in immature or ovariectomised mice, rats and monkeys. Thus, it appears to have antioestrogen activity without having any partial agonist (oestrogen-like) activity.

Fulvestrant inhibited the growth of the oestrogen-sensitive human breast cancer cell line MCF-7 *in vitro* and of xenografts of MCF-7 cells in nude mice. Fulvestrant inhibited the growth of tamoxifen-

resistant breast cancer cells *in vitro* and of tamoxifen-resistant breast tumours in nude mice.

Effects on breast cancer tissue in vivo:
Clinical trials in postmenopausal women with primary breast cancer have shown that fulvestrant significantly downregulates oestrogen receptor expression in oestrogen receptor positive tumours compared with placebo and tamoxifen. There was also a significant decrease in progesterone receptor expression consistent with the preclinical data demonstrating that fulvestrant lacks intrinsic oestrogen agonist activity. These changes in oestrogen receptor and progesterone receptor 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:
The preclinical data for fulvestrant suggest that it 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 micrograms per day ethinyl oestradiol. This demonstrates a potent antioestrogenic effect on the postmenopausal endometrium.

Clinical trials
Effects on advanced breast cancer
A Phase 3 clinical trial (CONFIRM) 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 (n = 362) with fulvestrant 250 mg (n = 374). Progression free survival (PFS) was the primary endpoint; key secondary efficacy endpoints included objective response rate (ORR); clinical benefit rate (CBR) and overall survival (OS). PFS for fulvestrant 500 mg was significantly longer than for fulvestrant 250 mg. Efficacy results are summarized in Table 3 and Figure 1 below. In the initial OS analysis after a minimum follow-up duration of 18 months, there was no statistically significant difference in OS between the two treatment groups. After a minimum follow-up duration of 50 months, an updated OS analysis was performed. Final OS analysis at 75% maturity showed that fulvestrant 500 mg was associated with a 4.1-month increase in median OS and a 19% reduction in the risk of death compared with fulvestrant 250 mg [HR=0.81; 95% CI 0.69-0.96; p = 0.016 (nominal p-value as no adjustment was made for multiplicity)].

Table 3 Efficacy results for the CONFIRM study: Intention To Treat Population

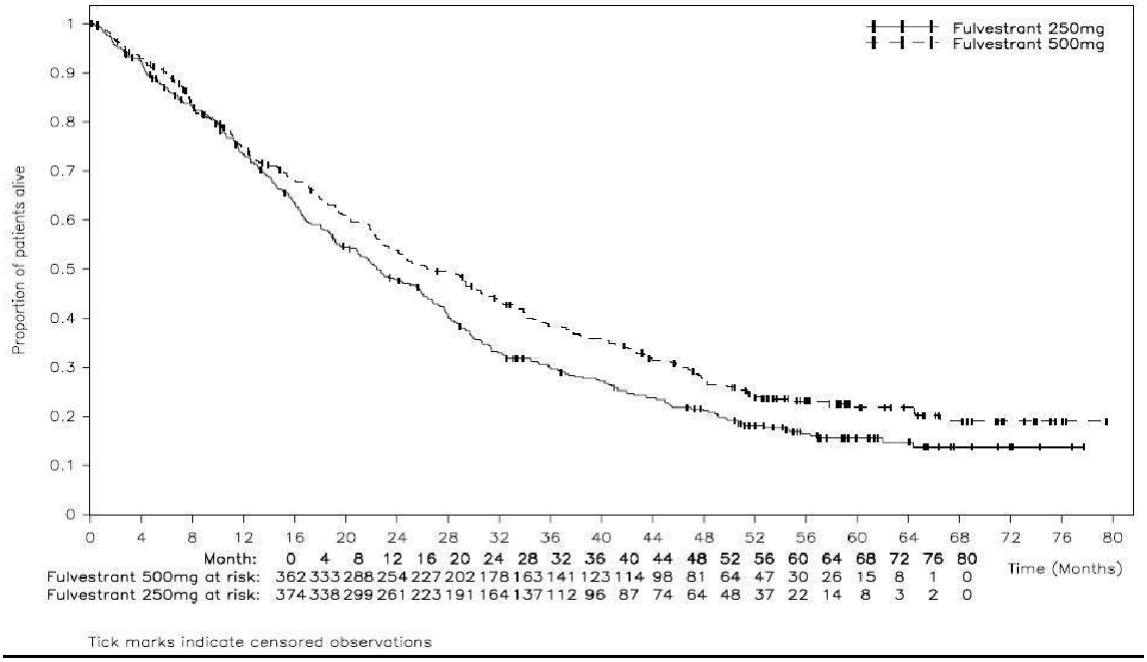
Endpoint	**Fulvestrant 500 mg (N = 362)**	**Fulvestrant 250 mg (N = 374)**
PFS[a] Median (months)	6.5	5.4
Hazard Ratio[b] (95% CI[c])	0.80 (0.68 – 0.94)	
p-value	0.006	
OS[d] Updated Analysis (% of patients who died)	261 (72.1%)	293 (78.3%)
Median OS (months)	26.4	22.3
Hazard Ratio[b] (95% CI[c])[f]	0.81 (0.69 – 0.96)	
ORR[g] (95% CI[c])	13.8% (9.7%, 18.8%) (33/240)	14.6% (10.5%, 19.4%) (38/261)

[a] PFS (Progression Free Survival) = the time between randomisation and the earliest of progression or death from any cause. Minimum follow-up duration of 18 months.
[b] Hazard ratio <1 favours fulvestrant 500 mg.
[c] CI = Confidence Interval [d] OS = Overall Survival [e] Minimum follow-up duration of 50 months.

[f] Not statistically significant as no adjustments were made for multiplicity.

[g] ORR (Objective Response Rate), defined as the number (%) of patients with complete or partial response, was analysed in the evaluable patients with measurable disease at baseline (fulvestrant 500 mg N = 240; fulvestrant 250 mg N = 261). Minimum follow- up duration of 18 months.

Figure 1 Kaplan-Meier plot of the updated Overall Survival data for the CONFIRM study



Irrespective of the last endocrine therapy (anti-oestrogen or aromatase inhibitor), the treatment effect (PFS) for fulvestrant 500 mg vs. fulvestrant 250 mg was consistent. There was no significant difference in CBR for patients receiving fulvestrant 500 mg vs 250 mg (45.6% vs 39.6%; odds ratio 1.28 [95% CI 0.95, 1.71]; p=0.1) or in duration of clinical benefit (median 16.6 vs 13.9 months for fulvestrant 500 mg and fulvestrant 250 mg, respectively).

Two Phase 3 clinical trials (Study 9238IL/0020 & 9238IL/0021) 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. These trials compared the safety and efficacy of fulvestrant with a third-generation aromatase inhibitor, anastrozole. Both trials used a dose of 250 mg every 28 days. The primary endpoint was progression free survival.

Overall, fulvestrant 250 mg was at least as effective as anastrozole in terms of progression free survival (PFS), objective response, clinical benefit, time to treatment failure and quality of life.

In Study 21, median PFS was 165 days with fulvestrant and 103 days with anastrozole (HR 0.92; 95% CI: 0.74 - 1.14). In Study 20, median PFS was 166 days with fulvestrant and 156 days with anastrozole (HR 0.98; 95% CI: 0.80 - 1.21)

Fulvestrant 250 mg had an ORR of 20.7% in Study 20 (vs 15.7% with anastrozole) and 17.5% in Study 21 (vs 17.5% with anastrozole).

Fulvestrant 250 mg showed durable responses in both trials. In Study 20, the median duration of response (DoR) was 19.3 months for fulvestrant 250 mg and 10.5 months for anastrozole. In Study 21, the median DoR was 14.3 months and 14.0 months for fulvestrant 250 mg and anastrozole 1 mg

respectively.

The majority of patients in these trials had ER+ and/or PgR+ tumors (about 80%). Patients who had ER-/PgR- or unknown disease must have shown prior response to endocrine therapy.

There are no efficacy data to support use of fulvestrant in premenopausal patients with advanced breast cancer.

FALCON (Study D699BC00001) was a Phase 3, randomised, double-blind, double-dummy, multicentre study of Fulvestrant versus anastrozole conducted in post-menopausal women with hormone receptor positive (oestrogen receptor positive and/or progesterone receptor positive) locally advanced or metastatic breast cancer who had not previously been treated with any endocrine therapy. A total of 462 patients were randomised 1:1 to receive Fulvestrant 500 mg intramuscularly on Days 1, 15, 29, and monthly thereafter, or anastrozole 1 mg orally daily. Randomisation was stratified by disease setting (locally advanced or metastatic), use of prior chemotherapy for advanced disease (yes or no), 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).

Patients enrolled in this study had a median age of 63 years (range 36-90). The majority of patients (87%) had metastatic disease at baseline. Fifty-five percent (55%) of patients had visceral metastasis at baseline. A total of 17% of patients received a prior chemotherapy regimen for advanced disease; 84% of patients had measurable disease. Sites of metastases were as follows: musculoskeletal 59%, lymph nodes 50%, respiratory 40%, liver (including gall bladder) 18%. For 10% of patients, musculoskeletal sites were the only sites of metastasis.

The results of the FALCON study are summarised in Table 4 and Figure 2. OS was not mature at the time of primary analysis. Consistent results for PFS were observed across the majority of pre specified patient subgroups. However, for the subgroup of patients with visceral metastasis (n=254), the hazard ratio (HR) for PFS was 0.993 (95% CI: 0.740, 1.331) for the Fulvestrant arm compared to the anastrozole arm. For the subgroup of patients with disease limited to non-visceral metastasis (n=208), the HR was 0.592 (95% CI: 0.419, 0.837) for the Fulvestrant arm compared to the anastrozole arm.

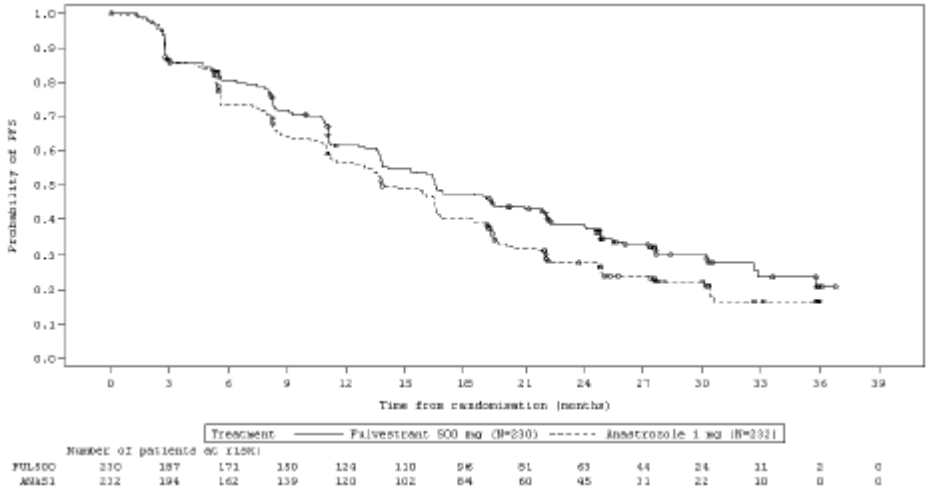
Table 4 Summary of results (intent-to-treat [ITT] population) by investigator assessment in the FALCON study

	Fulvestrant 500mg (N=230)	**Anastrozole 1mg (N=232)**
Progression-free survival (PFS)		
Number of PFS events (%)	143 (62.2%)	166 (71.6%)
Median PFS (months); 95% CI	16.6 (13.83 – 20.99)	13.8 (11.99 – 16.59)
PFS HR (95% CI) and p-value	HR 0.797 (0.637 -0.999) p = 0.0486	
Overall survival (OS)*		
Number of OS events	67 (29.1%)	75 (32.3%)
Median OS (months)	NR	NR
OS HR (95% CI) and p- value	HR 0.875 (0.629-1.217) P=0.4277	

Objective response rate (ORR) and duration of response(DOR)**		
ORR	89 (46.1%)	88 (44.9%)
Median DOR (Months)	20.0	13.2

HR = hazard ratio. NR = not reached.
*Interim analysis of OS performed with 61% of the total number of events required for final analysis (31% maturity)
**In patients with measurable disease

Figure 2 Kaplan-Meier plot of PFS by investigator assessment (ITT population) in the FALCON study



5.2 Pharmacokinetic properties

Absorption

After administration of fulvestrant long-acting intramuscular injection, fulvestrant is slowly absorbed and maximum plasma concentrations are reached after about 7 days. Absorption continues for over one month and monthly administration results in an approximate 2-fold accumulation. Steady-state levels are reached after about 6 doses during monthly injections with the major part of the accumulation achieved after 3-4 doses. The terminal half-life is governed by the absorption rate and was estimated to be 50 days. At steady state, fulvestrant plasma concentrations are maintained within a relatively narrow range with approximately 2- to 3-fold difference between maximum and trough concentrations.

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

Administration of fulvestrant 500 mg at day 0 and 14 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).

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. Very low density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL) fractions are the major binding components. Therefore, no drug interaction studies were conducted on competitive protein binding. The role of sex hormone-binding globulin has not been determined.

Metabolism
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 (includes 17-ketone, sulphone, 3-sulphate, 3- and 17-glucuronide metabolites). Identified metabolites are either less active or exhibit similar activity to fulvestrant in anti-oestrogen models. Studies using human liver preparations and recombinant human enzymes indicate that CYP 3A4 is the only P450 isoenzyme involved in the oxidation of fulvestrant, however non-P450 routes appear to be more predominant *in vivo*.

Excretion
Fulvestrant is eliminated mainly by metabolism. 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.

Special populations

Hepatic impairment
Fulvestrant is metabolized primarily in the liver. In clinical trials in patients with locally advanced or metastatic breast cancer, pharmacokinetic data were obtained following administration of a 250 mg dose of fulvestrant to 261 patients classified as having normal liver function and to 24 patients with mild impairment. Mild impairment was defined as an alanine aminotransferase concentration (at any visit) greater than the upper limit of the normal (ULN) reference range, but less than 2 times the ULN; or if any 2 of the following 3 parameters were between 1- and 2-times the ULN: aspartate aminotransferase, alkaline phosphatase, or total bilirubin.

There was no clear relationship between fulvestrant clearance and hepatic impairment and the safety profile in patients with mild hepatic impairment was similar to that seen in patients with no hepatic impairment. Safety and efficacy have not been evaluated in patients with moderate to severe hepatic impairment (see Sections 4.4 Special warnings and precautions for use and 4.2 Dosage and method of administration sections).

Renal Impairment
Negligible amounts of fulvestrant are eliminated in urine; therefore, a study in patients with renal impairment was not conducted. In the advanced breast cancer trials, fulvestrant concentrations in women with estimated creatinine clearance as low as 30 mL/min were similar to women with normal creatinine (see Section 4.4 Special warnings and precautions for use).

Other populations
No difference in fulvestrant pharmacokinetic profile was detected with regard to age (range 33 to 89 years).

No difference in fulvestrant pharmacokinetic profile was detected with regard to ethnic groups.

5.3 Preclinical safety data
Genotoxicity
Fulvestrant showed no genotoxic potential in bacterial reverse mutation assays, *in vitro* mouse lymphoma assays, an *in vitro* chromosome aberration assay in human lymphocytes, and an *in vivo* micronucleus assay in rats.

Carcinogenicity

A two-year rat oncogenicity study (intramuscular administration with the fulvestrant formulation) showed increased incidence of benign ovarian granulosa cell tumours in females at the high dose, 10 mg/rat/15 days (approx. 5-times the human dose based on plasma AUC values). Induction of such tumours is consistent with the pharmacology-related endocrine feedback alteration in gonadotropin levels caused by anti-oestrogen in cycling animals. Therefore, this finding is not considered to be clinically relevant to the use of fulvestrant in postmenopausal women with advanced breast cancer.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

FULVESTRANT EVER PHARMA contains ethanol, benzyl alcohol, benzyl benzoate and castor oil.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Store below 25ºC.Store in original pack.

6.5 Nature and contents of container

FULVESTRANT EVER PHARMA 250 mg/5 mL solution in pre-filled syringes (one (1) or two (2) syringes per pack).
Each pre-filled syringe consists of:

One 5 mL clear neutral glass (Type 1) barrel containing a nominal 5 mL of FULVESTRANT EVER PHARMA solution for injection and fitted with a tamper evident closure. The syringes are presented in a tray with polystyrene plunger rod and a safety needle (SafetyGlide™) for connection to the barrel.

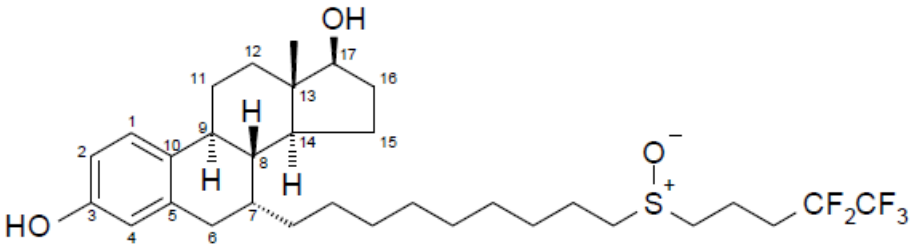
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

The chemical name is 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]estra-1,3,5(10)-triene-3,17β-diol.

Chemical structure



CAS number
129453-61-8

Molecular formula: $C_{32}H_{47}F_5O_3S$

MW: 606.8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

InterPharma Pty Ltd
Suite 103, 39 East Esplanade
MANLY NSW 2095

9 DATE OF FIRST APPROVAL

1 Oct 2021

10 DATE OF REVISION

Summary table of changes

Section changed	Summary of new information