# 1 PRODUCT NAME

Fulvestrant-AFT, 250 mg/5 mL, solution for injection

# 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 250 mg fulvestrant in 5 mL solution.

**Excipients with known effect (per 5 mL)**

Ethanol (96%, 500 mg)

Benzyl alcohol (500 mg)

Benzyl benzoate (750 mg)

For the full list of excipients see section 6.1.

# 3 PHARMACEUTICAL FORM

Solution for injection. Clear, colourless to yellow, viscous liquid.

# 4 CLINICAL PARTICULARS

## 4.1 Therapeutic indications

Fulvestrant-AFT is indicated for the treatment of locally advanced or metastatic breast cancer in postmenopausal women of any age previously treated with endocrine therapy (antioestrogen or aromatase inhibitor), irrespective of whether their postmenopausal status occurred naturally or was artificially induced.

## 4.2 Dose and method of administration

*Adult females (including the elderly)*

The recommended dose is 500 mg to be administered intramuscularly as two 5 mL injections, one in each buttock (gluteal area), at intervals of 1 month with an additional 500 mg dose given 2 weeks after the initial dose.

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

*Children*

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

*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).

*Patients with hepatic insufficiency*

No dose adjustments are recommended for patients with Child-Pugh category A and B hepatic impairment. The use of fulvestrant has not been evaluated in patients with Child-Pugh C hepatic impairment (see sections 4.4 and 5.2).

*Elderly*

No dose adjustment is required for elderly patients.

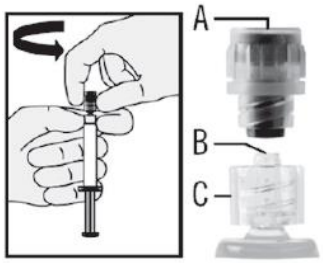
*Interactions requiring dose adjustments*

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

**Method of administration**

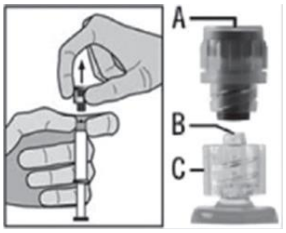
- Remove glass syringe barrel from tray and check that it is not damaged.
- Peel open the safety needle (SafetyGlide™) outer packaging.
- Inspect drug product in glass syringe for any visible particulate matter or discoloration prior to use. Discard if particulate matter or discoloration is present.
- Hold the syringe upright on the ribbed part (C). With the other hand, take hold of the cap (A) and carefully **twist the cap counter-clockwise** until the cap disconnect for removal (see Figure 1).

Figure 1



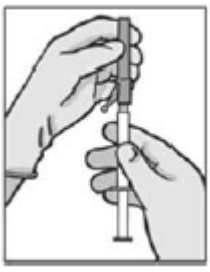

- Pull the cap (A) off in a straight upward direction. **Do not touch the sterile syringe tip** (Luer-Lok) (B) (see Figure 2).

Figure 2



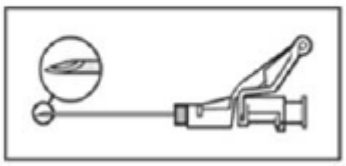

- Attach the safety needle to the syringe tip (Luer-Lok) and twist until firmly seated (see Figure 3).
- Confirm that needle is locked to the Luer connector before moving or tilting the syringe out of the vertical plane to avoid spillage of syringe contents.
- Pull shield straight off needle to avoid damaging needlepoint.
- 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 activate the lever arm to deploy the needle shieling by applying a single-finger stroke to the activation assisted lever arm to push the lever arm completely forward. Listen for a click. Confirm that the needle shielding has completely covered the needle (see Figure 5).
- NOTE: Activate away from self and others.

Figure 5

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

*Use in hepatic impairment*

Fulvestrant is metabolised primarily in the liver. Caution should be used with Fulvestrant-AFT in patients with hepatic impairment, as clearance may be reduced (see sections 4.2 and 5.2).

*Use in renal impairment*

Caution should be used before treating patients with creatinine clearance less than 30 mL/min (see section 5.2).

*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 injection. Caution should be taken while administering Fulvestrant-AFT at the dorsogluteal injection site due to the proximity of the underlying sciatic nerve (see sections 4.2 and 4.8).

## 4.5 Interaction with other medicines and other forms of interaction

Fulvestrant does not significantly inhibit any of the major cytochrome P450 (CYP) isoenzymes *in vitro*, and results from a clinical pharmacokinetic study 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. Results

from a clinical study with ketoconazole, a potent inhibitor of CYP3A4, also indicated that there is no clinically relevant change in fulvestrant clearance. Dosage adjustment is not necessary in patients co-prescribed CYP3A4 inhibitors or inducers.

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.

## 4.6 Fertility, pregnancy and lactation

*Pregnancy*

The use of Fulvestrant-AFT should be avoided in pregnant women. As expected with a potent antioestrogen, studies in animals have shown reproductive toxicity (see section 5.3). Patients of childbearing potential should use effective contraception during treatment with Fulvestrant-AFT and for 2 years after the last dose.

*Breast-feeding*

The use of Fulvestrant-AFT should be avoided in lactating women. Fulvestrant is found in rats' milk at levels significantly higher than those in rat plasma. The potential risk for humans is unknown.

*Fertility*

The effects of Fulvestrant-AFT on fertility in humans have not been studied. Refer section 5.3 for animal reproductive studies.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 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) alone that compared fulvestrant 500 mg with anastrozole 1 mg. Where frequencies differ between the pooled safety analysis and FALCON, the highest frequency is presented. The frequencies in the following table were based on all reported events, regardless of the investigator assessment of causality.

**Table 1: Summary of ADRs seen in clinical studies 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 | 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 | 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 Including more severe injection site related sciatica, neuralgia, neuropathic pain, and peripheral neuropathy.
b Based on any CTC grade change from baseline.
c 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 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, back pain, myalgia and pain in extremity.
e Frequency category differs between pooled safety dataset and FALCON.
f ADR was not observed in FALCON.

On the basis of the data, there is no evidence of a causal relationship between fulvestrant and uncommon or rare events reported in fulvestrant clinical studies

*Reporting of suspected adverse reactions*
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

## 4.9 Overdose

There are isolated reports of overdose with humans. If overdose occurs, this should be managed symptomatically. Animal studies suggest that no effects other than those related directly or indirectly to antioestrogenic activity were evident with higher doses of fulvestrant.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic antioestrogen, ATC Code: LO2BA03.

*Mechanism of action*

The pharmacology and mode of action studies established that fulvestrant is the first agent in a new class of antioestrogens that downregulate the oestrogen receptor (ER) and can therefore be described as an ER downregulator. Fulvestrant exerts its pharmacological effects by binding with high affinity to the oestrogen receptor alpha (ERα) and has a novel mode of action that induces a rapid loss of ERα protein from breast cancer cells.

Fulvestrant is a potent, reversible inhibitor of the growth of oestrogen-sensitive human breast cancer cells *in vitro* and has a greater potency and efficacy than tamoxifen. Fulvestrant inhibits the growth of oestrogen-sensitive xenografts of human breast cancer in nude mice, is more effective than tamoxifen in preventing the establishment of tumours from xenografts of human breast cancer cells and suppresses the growth of breast tumours for twice as long as tamoxifen. Fulvestrant inhibits the growth of tamoxifen-resistant breast cancer cells *in vitro* and of tamoxifen-resistant breast tumours *in vivo.*

*Effects on breast cancer tissue in vivo*

Clinical studies in postmenopausal women with primary breast cancer have shown that fulvestrant significantly downregulates ER expression in ER positive tumours in a dose dependent manner. There was also a significant decrease in progesterone receptor (PR) expression (a marker of oestrogen action) consistent with the preclinical data demonstrating that fulvestrant lacks intrinsic oestrogen 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.

*Clinical Efficacy and Safety*

*Effects on advanced breast cancer*

**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 | Fulvestrant 500 mg (N=362) | Fulvestrant 250 mg (N=374) | Comparison between groups (Fulvestrant 500 mg/ Fulvestrant 250 mg) | | |
|---|---|---|---|---|---|---|
| | | | | Hazard ratio | 95% CI | p-value |
| PFS | K-M median in months; hazard ratio | | | | | |
| All Patients | | 6.5 | 5.5 | 0.80 | 0.68, 0.94 | 0.006 |
| -AE subgroup (n=423) | | 8.6 | 5.8 | 0.76 | 0.62, 0.94 | 0.013 |
| -AI subgroup (n=313)[a] | | 5.4 | 4.1 | 0.85 | 0.67, 1.08 | 0.195 |
| Updated 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 | Fulvestrant 500 mg (N=362) | Fulvestrant 250 mg (N=374) | Comparison between groups (Fulvestrant 500 mg/ Fulvestrant 250 mg) | |
|---|---|---|---|---|---|
| | | | | Hazard ratio | 95% CI |
| ORR[d] | % of patients with OR; odds ratio | | | | |
| All Patients | | 13.8 | 14.6 | 0.94 | 0.57, 1.55 |
| -AE subgroup (n=296) | | 18.1 | 19.1 | 0.93 | 0.52, 1.68 |
| -AI subgroup (n=205)[a] | | 7.3 | 8.3 | 0.87 | 0.30, 2.44 |
| CBR[e] | % of patients with CB; odds ratio | | | | |
| All Patients | | 45.6 | 39.6 | 1.28 | 0.95, 1.71 |
| -AE subgroup (n=423) | | 52.4 | 45.1 | 1.34 | 0.92, 1.97 |
| -AI subgroup (n=313)[a] | | 36.2 | 32.3 | 1.19 | 0.74, 1.90 |

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

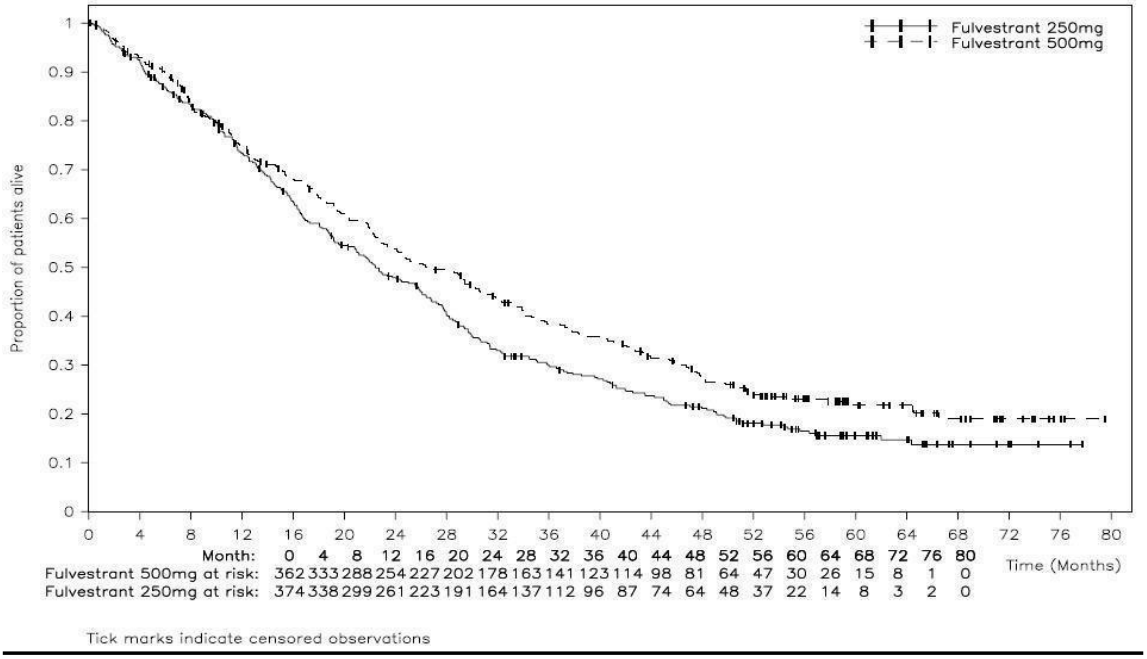
[b] OS is presented for the updated and final survival analyses at 75% maturity.

[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 (minimum follow-up duration of 50 months).

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

[e] Patients with a best objective response of complete response, partial response or stable disease ≥24 weeks. PFS:Progression-free survival (the time between randomization and the earliest of progression or death from any cause. Minimum follow-up duration of 18 months); ORR:Objective response rate; OR:Objective response; CBR:Clinical benefit rate; CB:Clinical benefit; OS:Overall survival; K-M:Kaplan-Meier; CI:Confidence interval; AI:Aromatase inhibitor; AE:Anti-oestrogen.

**Figure 6: Kaplan-Meier plot of the updated Overall Survival data for the CONFIRM study**




FALCON (Study D699BC00001) was a Phase 3, randomized, double-blind, double-dummy, multicentre study of fulvestrant 500 mg versus anastrozole 1 mg 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 randomized 1:1 to receive fulvestrant 500 mg or anastrozole 1 mg as hormonal treatment. This study compared the efficacy and safety of fulvestrant 500 mg and anastrozole 1 mg.

Randomization 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 Tumors). Key secondary efficacy endpoints included overall survival (OS), objective response rate (ORR), duration of response (DoR), expected duration of response (EDoR), clinical benefit rate (CBR), the duration of clinical benefit (DoCB), the expected duration of clinical benefit (EDoCB), and Health Related Quality of Life (HRQoL).

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. Sites of metastases occurred as follows: bone/locomotor 58.7%, lymph nodes 50.2%, respiratory 40.0%, liver (including gall bladder) 18.4%, and bone/locomotor only 10.4%.

A statistically significant improvement in PFS was observed for the fulvestrant arm compared to the anastrozole arm [HR=0.797 (95% CI: 0.637-0.999; 2-sided p=0.0486)]. The median PFS was 16.6 months (95% CI: 13.83, 20.99) in the fulvestrant arm and 13.8 months (95% CI: 11.99, 16.59) in the anastrozole arm. Consistent results were observed across the majority of pre-specified patient subgroups. For the subgroup of patients with disease limited to nonvisceral metastasis (n=208), the HR was 0.592 (95% CI: 0.419, 0.837) for the fulvestrant arm compared to anastrozole arm. For the subgroup of patients with visceral metastasis (n=254), the HR was 0.993 (95% CI: 0.740, 1.331) for the fulvestrant arm compared to anastrozole arm.

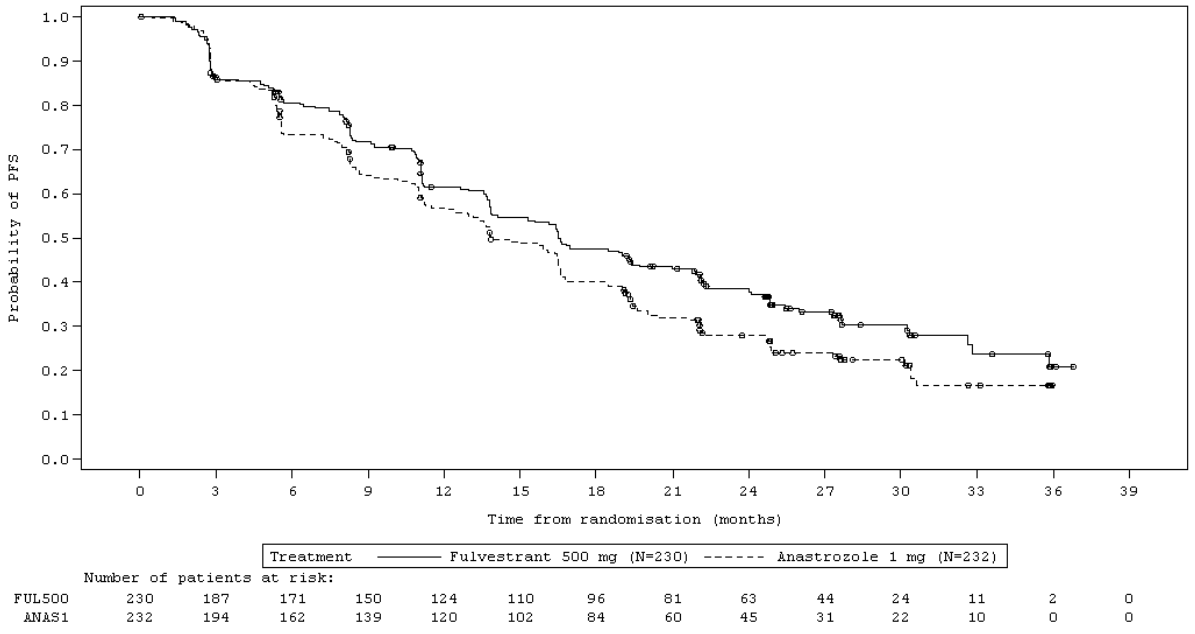
**Table 3: Summary of results of the primary efficacy endpoint (PFS) and key secondary efficacy endpoints (Investigator Assessment, Intent-To-Treat Population) – FALCON study**

| | **Fulvestrant 500 mg (N=230)** | **Anastrozole 1 mg (N=232)** |
|---|---|---|
| **Progression-Free Survival** | | |
| **Number of PFS Events (%)** | 143 (62.2%) | 166 (71.6%) |
| **PFS Hazard Ratio (95% CI) and p-value** | HR 0.797 (0.637- 0.999)<br>p = 0.0486 | |
| **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)<br>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)<br>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)<br>p = 0.3045 | |

*(31% maturity)-not final OS analysis

**for patients with measurable disease

**Figure 7: Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment, Intent-To-Treat Population) – FALCON Study**



Phase 3 clinical studies (Studies 9238IL/0020 and 9238IL/0021) compared the safety and efficacy of fulvestrant 250 mg with a third-generation aromatase inhibitor, anastrozole. The 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. In Study 9238IL/0021 the TTP for the comparison of fulvestrant 250 mg vs anastrozole was as follows: hazard ratio (95.14% CI) = 0.92 (0.74 to 1.14), p=0.43. In Study 9238IL/0020 the TTP for the comparison of fulvestrant 250 mg vs anastrozole was as follows: hazard ratio (95.14% CI) = 0.98 (0.80 to 1.21), p=0.84.

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

Fulvestrant 250 mg showed durable responses in both studies. In the North American study (Study 9238IL/0021), the median duration of response was 19.3 months for fulvestrant 250 mg and 10.5 months for anastrozole. In the rest of the world study (Study 9238IL/0020), the median duration of response was 14.3 and 14.0 months for fulvestrant 250 mg and anastrozole, respectively.

*Effects on the postmenopausal endometrium*

The preclinical data for fulvestrant suggest that it will not have a stimulatory effect on the postmenopausal endometrium. A study 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 oestradiol. This demonstrates a potent antioestrogenic effect on the postmenopausal endometrium.

Neoadjuvant 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. There is no evidence of adverse endometrial effects in the breast cancer patients studied.

*Effects on bone*

Neoadjuvant 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 is no evidence of adverse bone effects in the breast cancer patients studied.

## 5.2 Pharmacokinetic properties

Following intravenous or intramuscular administration, fulvestrant is rapidly cleared at a rate approximating to hepatic blood flow (nominally 10.5 mL plasma/min/kg). However, fulvestrant long-acting intramuscular injection maintains plasma fulvestrant concentrations within a narrow range (up to 3-fold) over a period of at least 28 days after injection. Administration of fulvestrant 500 mg 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).

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

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.

*Absorption*

Fulvestrant is not administered orally.

*Distribution*

Fulvestrant was subject to extensive and rapid distribution; the apparent volume of distribution at steady state was large (approximately 3 to 5 l/kg), which suggests that the compound distribution is largely extravascular. Fulvestrant was highly (99%) bound to plasma proteins at concentrations far in excess of those likely to be achieved in clinical use. 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 14C-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 antioestrogen 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*.

*Excretion*

Fulvestrant was rapidly cleared by the hepatobiliary route, the overall rate being determined by the mode of administration. Excretion was via the faeces and renal elimination of drug-related material was negligible (less than 1%).

*Special Populations*

*Hepatic insufficiency*

The pharmacokinetics of fulvestrant has been evaluated in a single-dose clinical study conducted in women with Child-Pugh category A and B hepatic impairment due to cirrhosis, using a high dose of a shorter duration intramuscular injection formulation. There was a 1.3 and 2-fold reduction in mean clearance in women with Child-Pugh category A and B hepatic impairment respectively compared to healthy women, which led to a similar fold increase in AUC. Child-Pugh category C women were not evaluated.

Modelled intramuscular mean steady state plasma concentrations of fulvestrant in women with Child-Pugh category A and B hepatic impairment fall within the upper range of concentrations expected for patients with normal hepatic function given the intra muscular formulation. Given the known safety profile of fulvestrant, no dose adjustment is considered to be necessary.

## 5.3 Preclinical safety data

*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.

*Chronic 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 antioestrogenic 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.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

- Ethanol 96%
- Benzyl alcohol
- Benzyl benzoate
- Castor oil

## 6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

## 6.3 Shelf life

48 months at 2 °C to 8 °C.
28 days when stored below 25 °C.

## 6.4 Special precautions for storage

Store at 2°C to 8°C (in a refrigerator). Do not freeze. Store in the original package in order to protect from light. Fulvestrant-AFT can be stored below 25 °C for up to 28 days. Do not return the unrefrigerated product back to the fridge.

## 6.5 Nature and contents of container

Fulvestrant-AFT 250 mg/5 mL solution in pre-filled syringes (two (2) syringes per pack). Each pre-filled syringe consists of one 5 mL clear glass barrel with PRTC Luer-Lok adaptor containing a nominal 5 mL of Fulvestrant-AFT solution for injection. 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

For administration instructions see Section 4.2 Dose and Method of Administration.

Discard used syringes into a sharps container.

Return unused and expired medicines to your local pharmacy for disposal.

## 7 MEDICINE SCHEDULE

Prescription Medicine

## 8 SPONSOR

AFT Pharmaceuticals Limited

PO Box 33-203

Takapuna

Auckland 0740

Phone: 0800 423 823

## 9 DATE OF FIRST APPROVAL

18 January 2024

## 10 DATE OF REVISION OF THE TEXT

18 January 2024

## SUMMARY TABLE OF CHANGES

| **Section changed** | **Summary of new information** |
|---|---|
| 4.2 | Method of administration updated |
| 6.3 | Shelf life extended to 48 months |