PACKAGE INSERT

(For the use of a Registered Medical Practitioner or a Hospital or Laboratory only.)

FULEVEX

(Fulvestrant Solution for Injection 250 mg/5 ml)

- **Qualitative and quantitative composition**

Each pre-filled syringe of 5 ml contains: Fulvestrant 250 mg.
For a full list of excipients, *see "List of excipients".*

- **Pharmaceutical Form**

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

- **Therapeutic indications**

Fulevex 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.

Combination therapy with palbociclib
Fulevex is indicated in combination with palbociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in women with disease progression following endocrine therapy.

- **Posology and method of administration**

Posology
Adult females (including the 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.

Combination therapy with palbociclib
When Fulevex is used in combination with palbociclib, refer to monotherapy recommended dose instruction for Fulevex. Refer to the prescribing information for palbociclib for Posology and method of administration.
Prior to the start of treatment with the combination of fulvestrant plus palbociclib, and throughout its duration, pre/perimenopausal women should be treated with LHRH agonists according to local clinical practice.

Special population
Paediatric patient:
Fulevex is not recommended for use in children or adolescents, as safety and efficacy have not been established in this age group.

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 Special warnings and precautions for use*).

Hepatic impairment:
No dose adjustments are recommended for patients with mild to moderate hepatic impairment. However, as fulvestrant exposure may be increased, Fulevex should be used with caution in these patients. There are no data in patients with severe hepatic impairment (*see Contraindications, Special warnings and precautions for use and Pharmacokinetic properties*).

- **Method of administration**

Fulevex 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 Fulevex at the dorsogluteal site due to the proximity of the underlying sciatic nerve.
For detailed instructions for administration, see "*Instructions for administration and Special precautions for disposal*".

- **Contraindications**

Hypersensitivity to the active substance, or to any of the other excipients.
Pregnancy and lactation (*see Pregnancy and lactation*).
Severe hepatic impairment (*see Special warnings and precautions for use and Pharmacokinetic Properties*).

Combination therapy with palbociclib
See palbociclib local Prescribing Information for Contraindications.

- **Special warnings and precautions for use**

Fulevex should be used with caution in patients with mild to moderate hepatic impairment (*see Posology and method of administration, Contraindications, and Pharmacokinetic properties*).
Fulevex should be used with caution in patients with severe renal impairment (creatinine clearance less than 30 ml/min) (*see Pharmacokinetic properties*).
Due to the intramuscular route of administration, Fulevex should be used with caution if treating patients with bleeding diatheses, thrombocytopenia or those taking anticoagulant treatment.
Injection site related events including sciatica, neuralgia, neuropathic pain, and peripheral neuropathy have been reported with Fulvestrant injection. Caution should be taken while administering Fulvestrant at the dorsogluteal injection site due to the proximity of the underlying sciatic nerve (*see Posology and method of administration and Undesirable effects*).
Thromboembolic events are commonly observed in women with advanced breast cancer and have been observed in clinical studies with Fulvestrant (*see Undesirable effects*). This should be taken into consideration when prescribing Fulvestrant to patients at risk.
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.

Fulvestrant can interfere with oestradiol measurement by immunoassay, resulting in falsely elevated oestradiol levels.

Combination therapy with palbociclib
See palbociclib local Prescribing Information for Special warnings and precautions for use.

- **Interactions with other medicinal products and other forms of interaction**

A clinical interaction study with midazolam (substrate of CYP 3A4) demonstrated that fulvestrant does not inhibit CYP 3A4. Clinical interaction studies with rifampicin (inducer of CYP 3A4) and ketoconazole (inhibitor of CYP 3A4) showed no clinically relevant change in fulvestrant clearance. Dose adjustment is therefore not necessary in patients who are receiving fulvestrant and CYP 3A4 inhibitors or inducers concomitantly.
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.

- **Fertility, pregnancy and lactation**

Women of child-bearing potential
Patients of child-bearing potential should be advised to use effective contraception while on treatment with fulvestrant and for 2 years after the last dose.
Pregnancy
Fulvestrant is contraindicated in pregnancy (*see Contraindications*). 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 Preclinical safety data*). If pregnancy occurs while taking Fulevex, 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 Fulevex. 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 Contraindications*).

Fertility
The effects of Fulvestrant on fertility in humans has not been studied.

- **Effects on ability to drive and use machines**

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

- **Undesirable effects**

Monotherapy
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 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.

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

SOC	**Very common ≥10%**	**Common ≥1 - <10 %**	**Uncommon ≥0.1% - <1 %**
Nervous system disorders		Headache	
Gastrointestinal disorders	Nausea	Vomiting, diarrhoea	
Infections and infestations		Urinary tract infections	
Skin and subcutaneous tissue disorders	Rash[e]		
Musculoskeletal and connective tissue disorders	Joint and musculoskeletal pain[d]	Back pain[a]	
Metabolism and nutrition disorders		Anorexia	
Vascular disorders	Hot flushes[e]	Venous thromboembolism[a]	
General disorders and administration site conditions	Asthenia[a], injection site reactions[b]	Neuropathy peripheral[e], sciatica[e]	Injection site haemorrhage[f], injection site haematoma[f], neuralgia[c,f]
Immune system disorders	Hypersensitivity reactions[e]		
Hepatobiliary disorders	Elevated hepatic enzymes (ALT, AST, ALP)[a]	Elevated bilirubin[a]	Hepatic failure[c,f], hepatitis[f], elevated gamma-GT[f]
Reproductive system and breast disorders		Vaginal haemorrhage[e]	Vaginal moniliasis[f], Leukorrhea[f]
Blood and lymphatic system		Reduced platelet count[e]	

[a] Includes adverse drug reactions for which the exact contribution of Fulvestrant cannot be assessed due to the underlying disease.

[b] The term injection site reactions does not include the terms injection site haemorrhage, injection site haematoma, sciatica, neuralgia and neuropathy peripheral.

[c] The event was not observed in major clinical studies (CONFIRM, 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, myalgia and pain in extremity.
[e] Frequency category differs between pooled safety dataset and FALCON.
[f] ADR was not observed in FALCON.

Description of selected adverse reactions
The descriptions included below are based on the safety analysis set of 228 patients who received at least one (1) dose of fulvestrant and 232 patients who received at least one (1) dose of anastrozole, respectively in the Phase 3 FALCON study.

Joint and musculoskeletal pain
In the FALCON study, the number of patients who reported an adverse reaction of joint and musculoskeletal pain was 65 (31.2%) and 48 (24.1%) for fulvestrant and anastrozole arms, respectively. Of the 65 patients in the Fulvestrant arm, 40% (26/65) of patients reported joint and musculoskeletal pain within the first month of treatment, and 66.2% (43/65) of patients within the first 3 months of treatment. No patients reported events that were CTCAE Grade ≥3 or that required a dose reduction, dose interruption, or discontinued treatment due to these adverse reactions.

Combination therapy with palbociclib
See palbociclib local Prescribing Information for Undesirable effects.

- **Overdose**

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

- **Pharmacodynamic properties**

Pharmacotherapeutic group: Endocrine therapy, antiestrogen, 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 down-regulation of estrogen receptor (ER) 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 safety and efficacy in advanced breast cancer
Fulvestrant Monotherapy

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 Fulvestrant 500 mg (n=362) with Fulvestrant 250 mg (n=374). Progression-free survival (PFS) was the primary endpoint; key secondary efficacy endpoints included objective response rate (ORR), clinical benefit rate (CBR) and overall survival (OS). Efficacy results for the CONFIRM study are summarized in Table 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	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**
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)**		
				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] Fulvestrant is indicated in patients whose disease had recurred or progressed on an antioestrogen 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 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; 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.

A Phase 3, randomised, double-blind, double-dummy, multicentre study of Fulvestrant 500 mg versus anastrozole 1 mg was conducted in postmenopausal women with ER-positive and/or PgR-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 Fulvestrant 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 Fulvestrant arm compared to the anastrozole arm. The efficacy results of the FALCON study are presented in Table 3 and Figure 1.

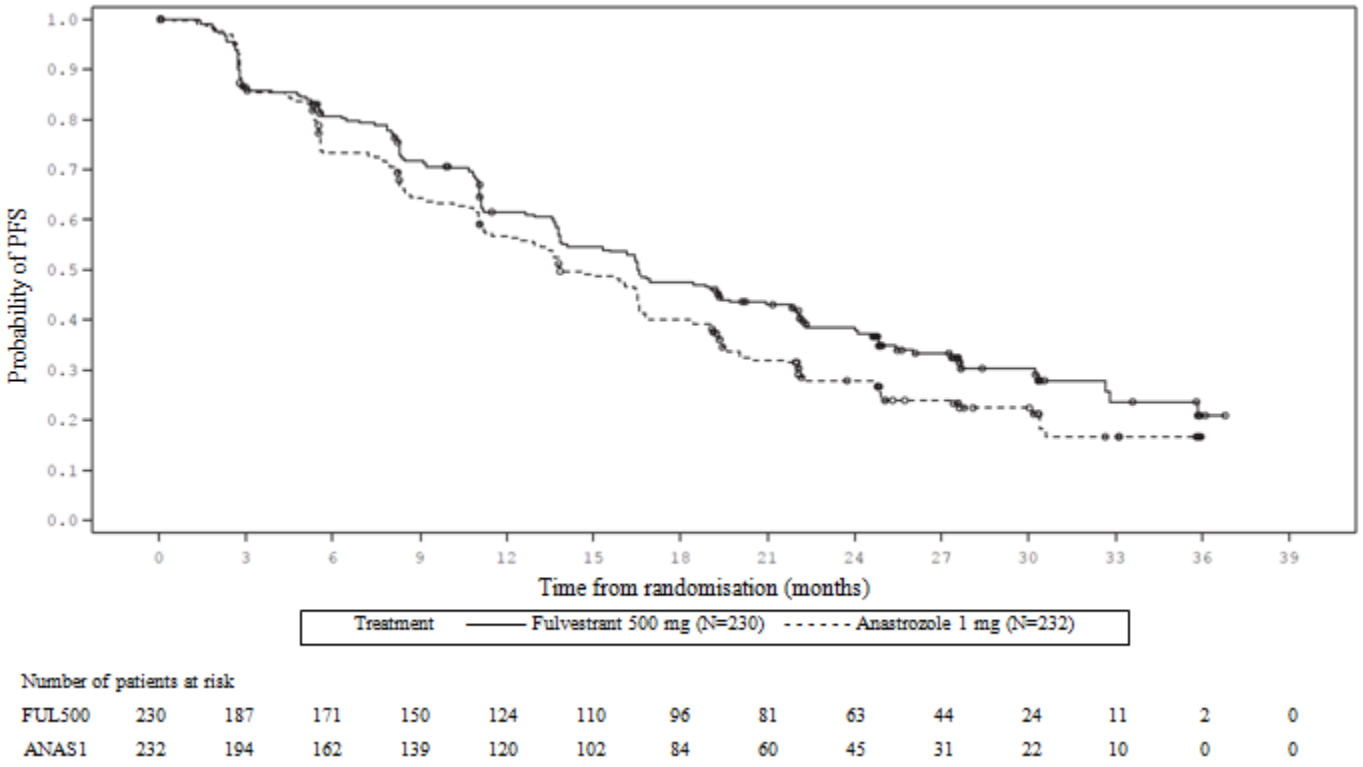
Table 3 Summary of results of the primary efficacy endpoint (PFS) and key secondary efficacy endpoints (Investigator Assessment, Intent-To-Treat Population) ─ FALCON study

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



Number of patients at risk

FUL500	230	187	171	150	124	110	96	81	63	44	24	11	2	0
ANAS1	232	194	162	139	120	102	84	60	45	31	22	10	0	0

Two Phase 3 clinical studies were completed in a total of 851 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. Seventy seven percent (77%) of the study population had estrogen receptor positive breast cancer. These studies compared the safety and efficacy of monthly administration of Fulvestrant 250 mg verses the daily administration of 1 mg anastrozole (aromatase inhibitor). Overall, Fulvestrant at the 250 mg monthly dose was at least as effective as anastrozole in terms of progression-free survival, objective response, and time to death. There were no statistically significant differences in any of these endpoints between the two treatment groups. Progression-free survival was the primary endpoint. Combined analysis of both studies showed that 83% of patients who received Fulvestrant progressed, compared with 85% of patients who received anastrozole.
Combined analysis of both studies showed the hazard ratio of Fulvestrant 250 mg to anastrozole for progression-free survival was 0.95 (95% CI 0.82 to 1.10). The objective response rate for Fulvestrant 250 mg was 19.2% compared with 16.5% for anastrozole. The median time to death was 27.4 months for patients treated with Fulvestrant and 27.6 months for patients treated with anastrozole. The hazard ratio of Fulvestrant 250 mg to anastrozole for time to death was 1.01 (95% CI 0.86 to 1.19).

<u>Combination therapy with palbociclib</u>
PALOMA-3 was a randomized, double-blind, parallel group, multicenter study of Fulvestrant 500 mg plus palbociclib 125 mg versus Fulvestrant 500 mg plus placebo conducted in women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative

locally advanced breast cancer not amenable to resection or radiation therapy with curative intent or metastatic breast cancer, regardless of their menopausal status, whose disease progressed after prior endocrine therapy in the (neo) adjuvant or metastatic setting.
A total of 521 pre/peri- and postmenopausal women who had progressed on or within 12 months from completion of adjuvant endocrine therapy or on or within 1 month from prior endocrine therapy for advanced disease, were randomized 2:1 to Fulvestrant plus palbociclib or Fulvestrant plus placebo and stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri- versus postmenopausal), and presence of visceral metastases. Pre/perimenopausal women received the LHRH agonist goserelin.
Patients with advanced/metastatic, symptomatic, visceral spread, that were at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement), were not eligible for enrolment into the study.
Patients continued to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. Crossover between treatment arms was not allowed.
Patients were well matched for baseline demographics and prognostic characteristics between the Fulvestrant plus palbociclib arm and the Fulvestrant plus placebo arm. The median age of patients enrolled in this study was 57 years (range 29, 88). In each treatment arm the majority of patients were White, had documented sensitivity to prior hormonal therapy, and were postmenopausal.
Approximately 20% of patients were pre/perimenopausal. All patients had received prior systemic therapy and most patients in each treatment arm had received a previous chemotherapy regimen for their primary diagnosis. More than half (62%) had an ECOG PS of 0, 60% had visceral metastases, and 60% had received more than 1 prior hormonal regimen for their primary diagnosis.
The primary endpoint of the study was investigator-assessed PFS evaluated according to RECIST 1.1. Supportive PFS analyses were based on an Independent Central Radiologic Review. Secondary endpoints included OS, OR, clinical benefit response (CBR), safety and time to deterioration (TTD) in pain endpoint.
The study met its primary endpoint of prolonging investigator-assessed PFS at the interim analysis conducted on 82% of the planned PFS events; the results crossed the pre-specified Haybittle-Peto efficacy boundary (α=0.00135), demonstrating a statistically significant prolongation in PFS and a clinically meaningful treatment effect. A more mature update of efficacy data is reported in Table 4.

After a median follow-up time of 45 months, the final OS analysis was performed based on 310 events (60% of randomised patients). A 6.9-month difference in median OS in the palbociclib plus fulvestrant arm compared with the placebo plus fulvestrant arm was observed; this result was not statistically significant at the prespecified significance level of 0.0235 (1-sided). In the placebo plus fulvestrant arm, 15.5% of randomised patients received palbociclib and other CDK inhibitors as post-progression subsequent treatments.
The results from the investigator-assessed PFS and final OS data from PALOMA3 study are presented in Table 4. The relevant Kaplan-Meier plots are shown in Figures 2 and 3, respectively.

Table 4 Efficacy results – PALOMA3 study (Investigator assessment, intent-to-treat population)

	Updated Analysis (23 October 2015 cut-off)	
	Fulvestrant plus palbociclib (N=347)	**Fulvestrant plus placebo (N=174)**
Progression-Free Survival		
Median [months (95% CI)]	11.2 (9.5, 12.9)	4.6 (3.5, 5.6)
Hazard ratio (95% CI) and p-value	0.497 (0.398, 0.620), p <0.000001	
Secondary end points*		
OR [% (95% CI)]	21.0 (16.9, 25.7)	8.6 (4.9, 13.8)
OR (measurable disease) [% (95% CI)]	27.3 (22.1, 33.1)	10.9 (6.2, 17.3)
DOR (measurable disease) [months (95% CI)]	10.4 (8.3, NE)	9.0 (5.6, NE)
CBR [% (95% CI)]	66.3 (61.0, 71.2)	39.7 (32.3, 47.3)

Final overall survival (OS) (13 April 2018 cutoff)		
Number of events (%)	201 (57.9)	109 (62.6)
Median [months (95% CI)]	34.9 (28.8, 40.0)	28.0 (23.6, 34.6)
Hazard ratio (95% CI) and p-value	0.814 (0.644, 1.029) p =0.0857 † *	

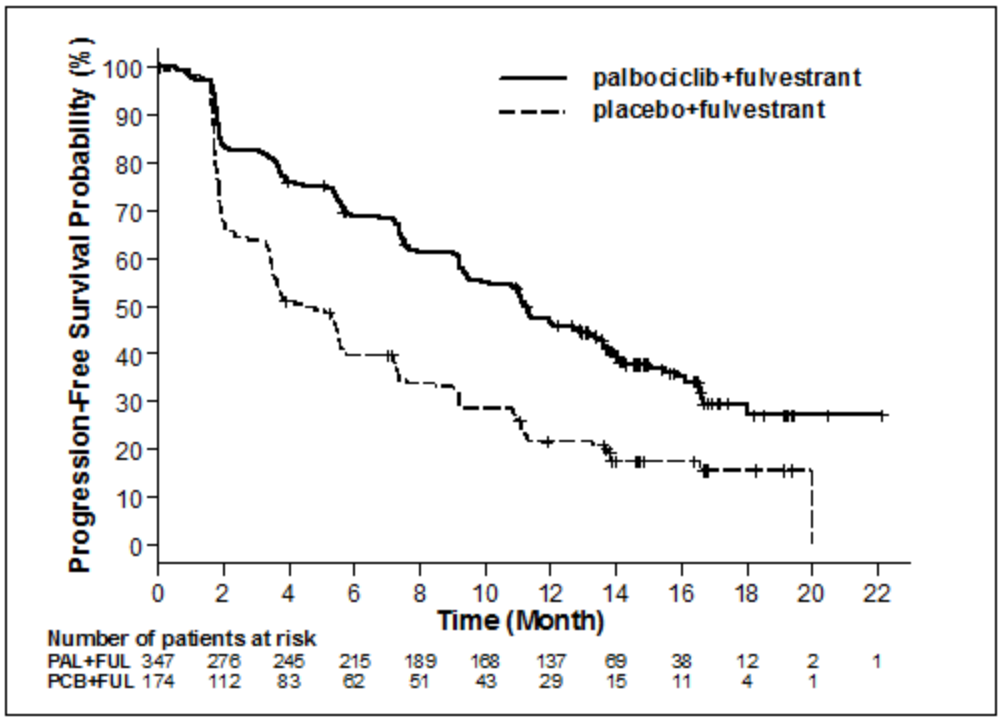
*Response endpoints based on confirmed responses.

N=number of patients; CI=confidence interval; NE=not estimable; OR=objective response; CBR=clinical benefit response; DOR=duration of response; PFS=progression-free-survival

Secondary endpoint results are based on confirmed and unconfirmed responses according to RECIST 1.1.
*Not statistically significant at the pre-specified 2-sided alpha level of 0.047.

† 2-sided p-value from the log-rank test stratified by the presence of visceral metastases and sensitivity to prior endocrine therapy per randomisation.

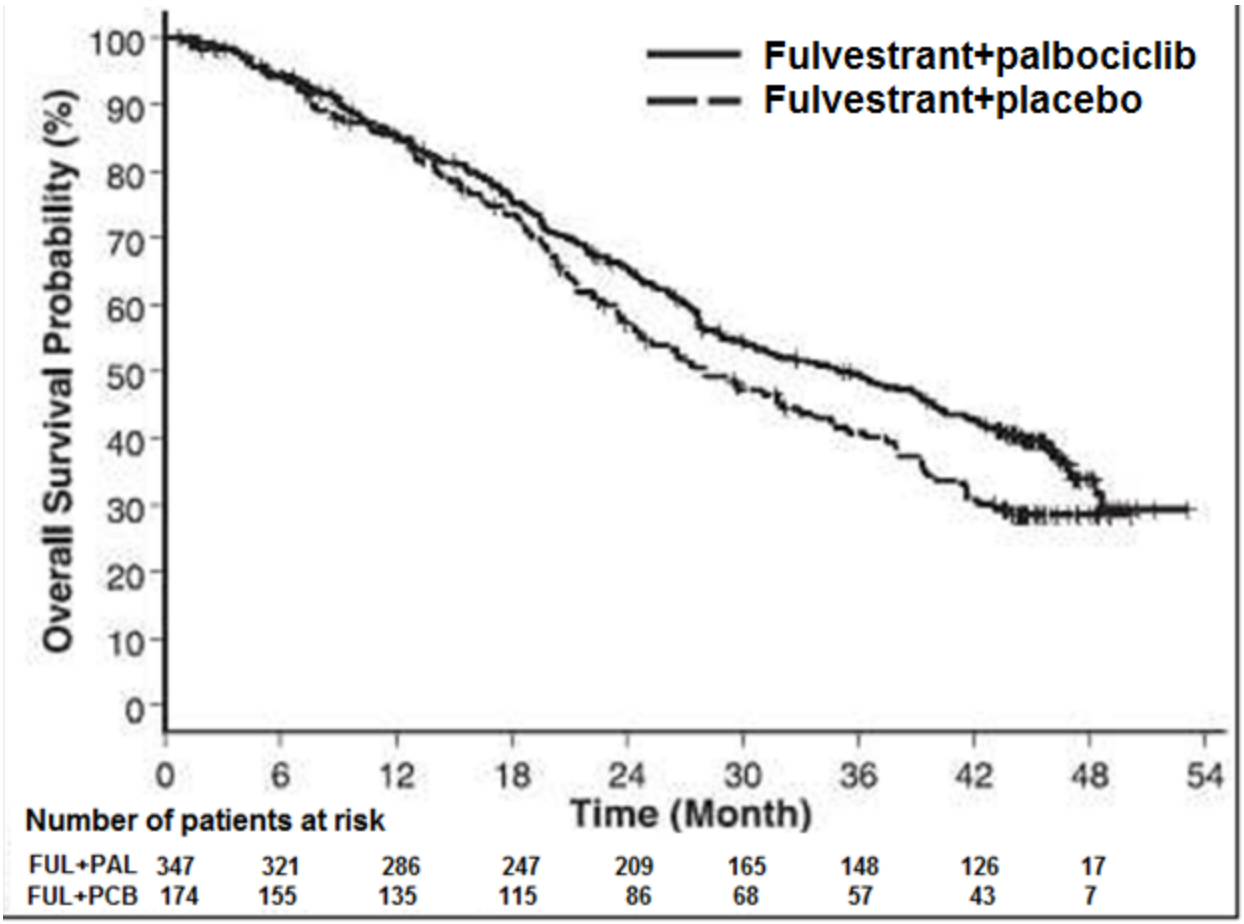
Figure 2 Kaplan-Meier plot of progression-free survival (investigator assessment, intent-to-treat population) – PALOMA3 study (23 October 2015 cutoff)



FUL=fulvestrant; PAL=palbociclib; PCB=placebo.

A reduction in the risk of disease progression or death in the Fulvestrant plus palbociclib arm was observed in all individual patient subgroups defined by stratification factors and baseline characteristics. This was evident for pre/perimenopausal women (HR of 0.46 [95% CI: 0.28, 0.75]) and postmenopausal women (HR of 0.52 [95% CI: 0.40, 0.66]) and patients with visceral site of metastatic disease (HR of 0.50 [95% CI: 0.38, 0.65]) and non-visceral site of metastatic disease (HR of 0.48 [95% CI: 0.33, 0.71]). Benefit was also observed regardless of lines of prior therapy in the metastatic setting, whether 0 (HR of 0.59 [95% CI: 0.37, 0.93]), 1 (HR of 0.46 [95% CI: 0.32, 0.64]), 2 (HR of 0.48 [95% CI: 0.30, 0.76]), or ≥3 lines (HR of 0.59 [95% CI: 0.28, 1.22]).

Figure 3 Kaplan-Meier plot of overall survival (intent-to-treat population) – PALOMA3 study (13 April 2018 cutoff)



FUL=Fulvestrant; PAL=palbociclib; PCB=placebo.

Patient-reported symptoms were assessed using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and its Breast Cancer Module (EORTC QLQ-BR23). A total of 335 patients in the Fulvestrant plus palbociclib arm and 166 patients in the Fulvestrant plus placebo arm completed the questionnaire at baseline and at least 1 post-baseline visit.

Time-to-Deterioration was pre-specified as time between baseline and first occurrence of ≥10 points increase from baseline in pain symptom scores. Addition of palbociclib to Fulvestrant resulted in a symptom benefit by significantly delaying time-to-deterioration in pain symptom compared with Fulvestrant plus placebo (median 8.0 months versus 2.8 months; HR of 0.64 [95% CI: 0.49, 0.85]; p<0.001).

Effects on the postmenopausal endometrium

Preclinical data do not suggest a stimulatory effect of fulvestrant on the postmenopausal endometrium (*see Preclinical safety data*). A 2-week study in healthy postmenopausal volunteers treated with 20 µg per day of ethinylestradiol showed that pre-treatment with Fulvestrant 250 mg resulted in significantly reduced stimulation of the postmenopausal endometrium, compared to pre-treatment with placebo, as judged by ultrasound measurement of endometrium thickness.

Neoadjuvant treatment for up to 16 weeks in breast cancer patients treated with either Fulvestrant 500 mg or Fulvestrant 250 mg did not result in clinically significant changes in endometrial thickness, indicating a lack of agonist effect. There is no evidence of adverse endometrial effects in the breast cancer patients studied. No data are available regarding endometrial morphology.
In two short-term studies (1 and 12 weeks) in premenopausal patients with benign gynaecologic disease, no significant differences in endometrial thickness were observed by ultrasound measurement between fulvestrant and placebo groups.
Effects on bone
There are no long-term data on the effect of fulvestrant on bone. Neoadjuvant treatment for up to 16 weeks in breast cancer patients with either Fulvestrant 500 mg or Fulvestrant 250 mg did not result in clinically significant changes in serum bone-turnover markers.

- **Pharmacokinetic properties**

Absorption:
After administration of Fulvestrant long-acting intramuscular injection, fulvestrant is slowly absorbed and maximum plasma concentrations (Cmax) are reached after about 5 days.
Administration of Fulvestrant 500 mg regimen achieves exposure levels at, or close to, steady state within the first month of dosing (mean [CV]: AUC 475 [33.4%] ng.days/ml, Cmax 25.1 [35.3%] ng/ml, Cmin 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 (Vdss) 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.

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.
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 CYP 3A4 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 (t1/2) 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 women. In patients administered Fulvestrant, an increase in exposure of this magnitude is expected to be well tolerated. Women with severe hepatic impairment (Child-Pugh class C) were not evaluated.

- **Preclinical safety data**

The acute toxicity of fulvestrant is low.
Fulvestrant and other formulations of fulvestrant were well tolerated in animal species used in multiple dose studies. Local reactions, including myositis and granulomata at the injection site were attributed to the vehicle but the severity of myositis in rabbits increased with fulvestrant, compared to the saline control. In toxicity studies with multiple intramuscular doses of fulvestrant in rats and dogs, the 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 (Cmax >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 Fulvestrant) showed increased incidence of ovarian benign granulosa cell tumours in female rats at the high dose, 10 mg/rat/15 days and an increased incidence of testicular Leydig cell tumours in males. In a two-year mouse oncogenicity study (daily oral administration) there was an increased incidence of ovarian sex cord stromal tumours (both benign and malignant) at doses of 150 and 500 mg/kg/day. At the no-effect level for these findings, systemic exposure levels (AUC) were, in rats,

approximately 1.5–fold the expected human exposure levels in females and 0.8-fold in males, and in mice, approximately 0.8-fold the expected human exposure levels in both males and females. Induction of such tumours is consistent with pharmacology related endocrine feedback alterations in gonadotropin levels caused by 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.

- **List of excipients**

Ethanol 96%
Benzyl alcohol
Benzyl benzoate
Refined Castor oil

- **Incompatibilities**

In the absence of incompatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life: 24 months

Special precautions for storage:
Store at 2°C-8°C (in a refrigerator).
Store the pre-filled syringe in the original package in order to protect from light.

Pack size: Fulvestrant Injection 50 mg/mL is supplied as ONE 5 mL clear glass (Type 1) barrel containing 250 mg/5 mL of Fulvestrant solution for intramuscular injection and fitted with a tamper evident closure. The syringes are presented in a tray with plunger rod and safety needles (Safety Glide Needle) for connection to the barrel.
Instructions for administration and Special precautions for disposal and other handling

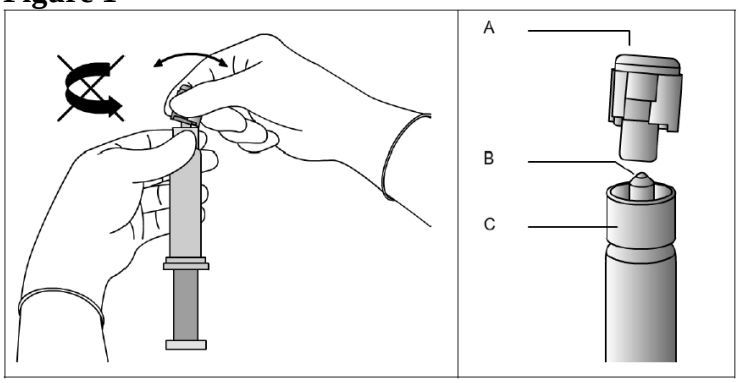
Administer the injection according to the local guidelines for performing large volume intramuscular injections.
NOTE: Due to the proximity of the underlying sciatic nerve, caution should be taken if administering Fulvestrant injection at the dorsogluteal injection site (*see Special warnings and precautions for use*)
Warning - Do not autoclave safety needle (BD SafetyGlide™ Shielding Hypodermic Needle) before use. Hands must remain behind the needle at all times during use and disposal.

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

For each syringe:
1. Remove glass syringe barrel from tray and check that it is not damaged.
2. Remove perforated patient record label from syringe.
3. Inspect drug product in glass syringe for any visible particulate matter or discoloration prior to use. Discard if particulate matter or discoloration is present.
4. Peel open the safety needle (SafetyGlide™) outer packaging.

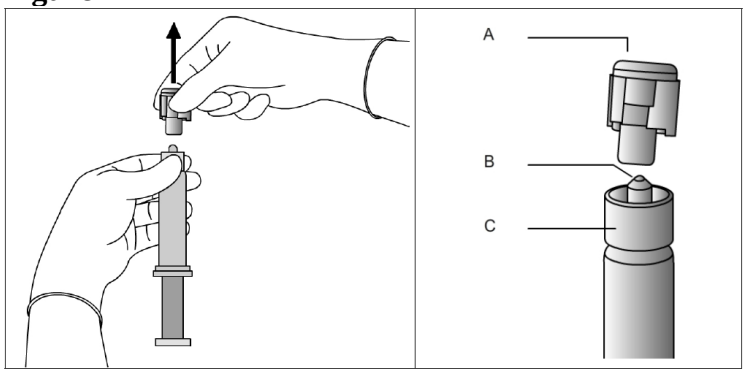
5. Hold the syringe upright on the ribbed part (C). With the other hand, take hold of the cap (A) and carefully tilt cap back and forth (DO NOT TWIST CAP) until the cap disconnects for removal (see Figure 1).

Figure 1



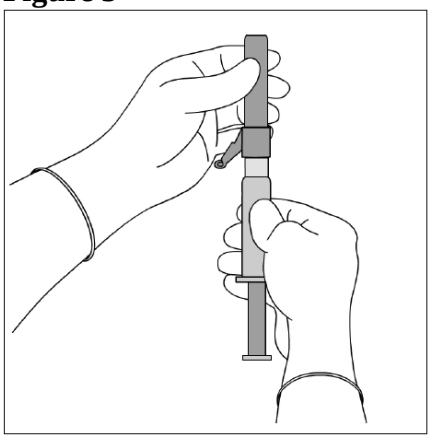
6. Pull the cap (A) off in a straight upward direction. DO NOT TOUCH THE STERILE SYRINGE TIP (Luer-Lok) (B) (see Figure 2).

Figure 2



7.
Attach the safety needle to the syringe tip (Luer-Lok) and twist until firmly seated (see Figure 3). Confirm that the needle is locked to the Luer connector before moving or tilting the syringe out of the vertical plane to avoid spillage of syringe contents.

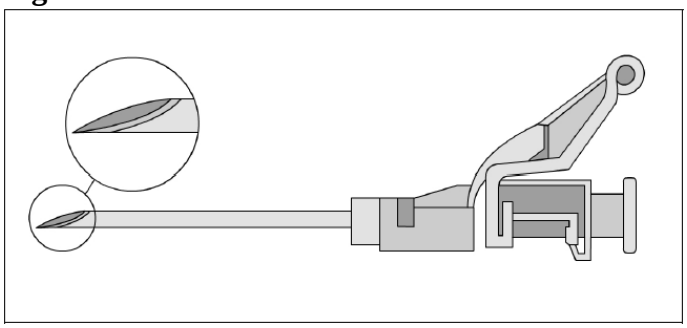
Figure 3



For Administration:

8. Pull shield straight off needle to avoid damaging needle point.
9. Remove needle sheath.
10. Expel excess gas from the syringe (a small gas bubble may remain).
11. Administer intramuscularly slowly (1-2 minutes/injection) into the buttock (gluteal area). For user convenience, the needle 'bevel up' position is orientated to the lever arm, as shown in Figure 4.

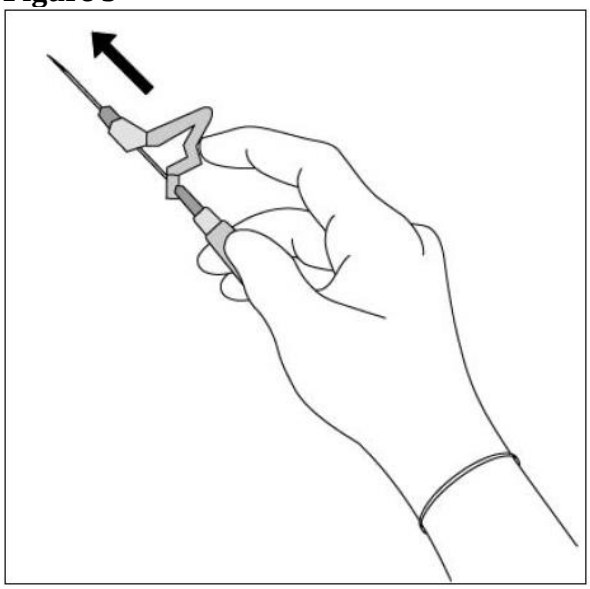
Figure 4



12. 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



13. Discard the empty single use syringe into an approved sharps collector in accordance with applicable regulations and institutional policy.

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.

- **Product registrant**

DKSH Singapore Pte. Ltd.
47 Jalan Buroh #09-01
Singapore 619491

- **Date of Revision of Package Insert**

October 2022