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Press Release

Hikma launches Fulvestrant Injection

London, 20 September, 2022 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Fulvestrant Injection, 250mg/5mL, in the US. The drug is indicated for the treatment of hormone-receptor (HR) positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women.

According to IQVIA, US sales of Fulvestrant Injection, 250mg/5mL, were approximately $105 million in the 12 months ending June 2022.

- ENDS -

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About Hikma
(LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated BBB-/stable S&P and BBB-/stable Fitch)

Hikma helps put better health within reach every day for millions of people around the world. For more than 40 years, we've been creating high-quality medicines and making them accessible to the people who need them. Headquartered in the UK, we are a global company with a local presence across the United States (US), the Middle East and North Africa (MENA) and Europe, and we use our unique insight and expertise to transform cutting-edge science into innovative solutions that transform people's lives. We're committed to our customers, and the people they care for, and by thinking creatively and acting practically, we provide them with a broad range of branded and non-branded generic medicines. Together, our 8,700 colleagues are helping to shape a healthier world that enriches all our communities. We are a leading licensing partner, and through our venture capital arm, are helping bring innovative health technologies to people around the world. For more information, please visit: www.hikma.com

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Important Safety Information for Fulvestrant Injection, 250mg/5mL:

CONTRAINDICATIONS

Fulvestrant is contraindicated in patients with a known hypersensitivity to the drug or to any of its components. Hypersensitivity reactions, including urticaria and angioedema, have been reported in association with fulvestrant *[see Adverse Reactions (6.2)]*.

WARNINGS & PRECAUTIONS

- **Risk of Bleeding:** Because fulvestrant is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use.
- **Increased Exposure in Patients with Hepatic Impairment:** The safety and pharmacokinetics of fulvestrant were evaluated in a study in seven subjects with moderate hepatic impairment (Child-Pugh class B) and seven subjects with normal hepatic function. Exposure was increased in patients with moderate hepatic impairment, therefore, a dose of 250mg is recommended *[see Dosage and Administration (2.2)]*. Fulvestrant has not been studied in patients with severe hepatic impairment (Child-Pugh class C) *[see Use in Specific Populations (8.6)]*.
- **Injection Site Reaction:** 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 Dosage and Administration (2.3)* and *Adverse Reactions (6.1)]*.
- **Embryo-Fetal Toxicity:** Based on findings from animal studies and its mechanism of action, fulvestrant can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of fulvestrant to pregnant rats and rabbits during organogenesis resulted in embryo-fetal toxicity at daily doses that are significantly less than the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with fulvestrant and for one year after the last dose *[see Use in Specific Populations (8.1), (8.3)* and *Clinical Pharmacology (12.1)]*.
- **Immunoassay Measurement of Serum Estradiol:** Due to structural similarity of fulvestrant and estradiol, fulvestrant can interfere with estradiol measurement by immunoassay, resulting in falsely elevated estradiol levels.

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Risk of Bleeding *[see Warnings and Precautions (5.1)]*
- Increased Exposure in Patients with Hepatic Impairment *[see Warnings and Precautions (5.2)]*
- Injection Site Reaction *[see Warnings and Precautions (5.3)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.4)]*

Most Common Adverse Drug Reactions

The most common adverse reactions reported (≥20%) in the fulvestrant plus abemaciclib arm were diarrhea, fatigue, neutropenia, nausea, infections, abdominal pain, anemia, leukopenia, decreased appetite, vomiting, and headache (Table 7 of the package insert, laboratory abnormalities are listed in Table 8 of the package insert).

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

Refer to package insert for full list of clinical trials adverse reactions, including those associated with dose reduction, permanent study treatment discontinuation, most common, most frequently reported, and additional adverse reactions.

Monotherapy

Comparison of Fulvestrant 500 mg and Fulvestrant 250 mg (CONFIRM)

Adverse reactions (ARs) were calculated based on the safety analysis of CONFIRM comparing the administration of fulvestrant 500 mg intramuscularly once a month with fulvestrant 250 mg intramuscularly once a month. Table 1 of the package insert lists adverse reactions reported with an incidence of 5% or greater, regardless of assessed causality, from CONFIRM.

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Comparison of Fulvestrant 500 mg and Anastrozole 1 mg (FALCON)
The safety of fulvestrant 500 mg versus anastrozole 1 mg was evaluated in FALCON. The data described in the package insert reflect exposure to fulvestrant in 228 out of 460 patients with HR-positive advanced breast cancer in postmenopausal women not previously treated with endocrine therapy who received at least one (1) dose of treatment in FALCON. Adverse reactions reported in patients who received fulvestrant in FALCON at an incidence of ≥5% in either treatment arm are listed in Table 2 of the package insert, and laboratory abnormalities are listed in Table 3 of the package insert.

Comparison of Fulvestrant 250 mg and Anastrozole 1 mg in Combined Trials (Studies 0020 and 0021)
Table 4 of the package insert lists adverse reactions 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.

Combination Therapy
Combination Therapy with Palbociclib (PALOMA-3)
The safety of fulvestrant 500 mg plus palbociclib 125 mg per day versus fulvestrant plus placebo was evaluated in PALOMA-3. The data described in the package insert reflect exposure to fulvestrant plus palbociclib in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of treatment in PALOMA-3. The median duration of treatment for fulvestrant plus palbociclib was 10.8 months while the median duration of treatment for fulvestrant plus placebo arm was 4.8 months.

No dose reduction was allowed for fulvestrant in PALOMA-3. Dose reductions of palbociclib due to an adverse reaction of any grade occurred in 36% of patients receiving fulvestrant plus palbociclib.

Adverse reactions (≥10%) reported in patients who received fulvestrant plus palbociclib or fulvestrant plus placebo in PALOMA-3 are listed in Table 5 of the package insert, and laboratory abnormalities are listed in Table 6 of the package insert.

Combination Therapy with Abemaciclib (MONARCH 2)
The safety of fulvestrant (500 mg) plus abemaciclib (150 mg twice daily) versus fulvestrant plus placebo was evaluated in MONARCH 2. The data described in the package insert reflect exposure to fulvestrant in 664 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of fulvestrant plus abemaciclib or placebo in MONARCH 2.

Median duration of treatment was 12 months for patients receiving fulvestrant plus abemaciclib and 8 months for patients receiving fulvestrant plus placebo.

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 18 cases (4%) of fulvestrant plus abemaciclib treated patients versus 10 cases (5%) of fulvestrant plus placebo treated patients. Causes of death for patients receiving fulvestrant plus abemaciclib included: 7 (2%) patient deaths due to underlying disease, 4 (0.9%) due to sepsis, 2 (0.5%) due to pneumonitis, 2 (0.5%) due to hepatotoxicity, and one (0.2%) due to cerebral infarction.

Combination Therapy with Ribociclib (MONALEESA-3)
The safety of fulvestrant 500 mg plus ribociclib 600 mg versus fulvestrant plus placebo was evaluated in MONALEESA-3. The data described in the packager insert reflect exposure to fulvestrant plus ribociclib in 483 out of 724 postmenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy who received at least one dose of fulvestrant plus ribociclib or placebo in MONALEESA-3. Median duration of treatment was 15.8 months for fulvestrant plus ribociclib and 12 months for fulvestrant plus placebo.

Adverse reactions and laboratory abnormalities occurring in patients in MONALEESA-3 are listed in Table 9 and Table 10 of the package insert, respectively.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of fulvestrant. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

For fulvestrant 250 mg, other adverse reactions reported as drug-related and seen infrequently (<1%) include thromboembolic phenomena, myalgia, vertigo, leukopenia, and hypersensitivity reactions, including angioedema and urticaria.

Vaginal bleeding has been reported infrequently (<1%),mainly in patients during the first 6weeks after changing from existing hormonal therapy to treatment with fulvestrant. If bleeding persists, further evaluation should be considered.

Elevation of bilirubin, elevation of gamma GT, hepatitis, and liver failure have been reported infrequently (<1%).

DRUG INTERACTIONS

There are no known drug-drug interactions. Although, fulvestrant is metabolized by CYP 3A4 *in vitro*, drug interactions studies with ketoconazole or rifampin did not alter fulvestrant pharmacokinetics. Dose adjustment is not needed in patients co-prescribed CYP 3A4 inhibitors or inducers *[see Clinical Pharmacology (12.3)]*.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
Based on findings from animal studies and its mechanism of action, fulvestrant can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data in pregnant women to inform the drug-associated risk.

Lactation
Risk Summary
There is no information regarding the presence of fulvestrant in human milk, nor of its effects on milk production or breastfed infant. Fulvestrant can be detected in rat milk *[see Data]*. Because of the potential for serious adverse reactions in breastfed infants from fulvestrant, advise a lactating woman not to breastfeed during treatment with fulvestrant and for one year after the final dose.

Females and Males of Reproductive Potential
Pregnancy testing is recommended for females of reproductive potential within seven days prior to initiating fulvestrant. Fulvestrant can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment and for one year after the last dose. Based on animal studies, fulvestrant may impair fertility in females and males of reproductive potential. The effects of fulvestrant on fertility were reversible in female rats *[see Nonclinical Toxicology (13.1)]*.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
For fulvestrant 250 mg, when tumor response was considered by age, objective responses were seen in 22% and 24% of patients under 65 years of age and in 11% and 16% of patients 65 years of age and older, who were treated with fulvestrant in Study 0021 and Study 0020, respectively.

Hepatic Impairment
Fulvestrant is metabolized primarily in the liver. A dose of fulvestrant 250 mg is recommended in patients with moderate hepatic impairment (Child- Pugh class B) *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2)]*.

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.

DOSAGE AND ADMINISTRATION

Recommended Dose

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Monotherapy
The recommended dose of fulvestrant injection is 500 mg to be administered intramuscularly into the buttocks (gluteal area) slowly (1 to 2minutes per injection) as two 5mL injections, one in each buttock, on Days 1, 15, 29, and once monthly thereafter *[see Clinical Studies (14)]*.

Combination Therapy
When fulvestrant injection is used in combination with palbociclib, abemaciclib, or ribociclib, the recommended dose of fulvestrant injection is 500 mg to be administered intramuscularly into the buttocks (gluteal area) slowly (1 to 2 minutes per injection) as two 5 mL injections, one in each buttock, on Days 1, 15, 29, and once monthly thereafter.

When fulvestrant injection is used in combination with palbociclib, the recommended dose of palbociclib is a 125mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Palbociclib should be taken with food. Refer to the Full Prescribing Information for palbociclib.

When fulvestrant injection is used in combination with abemaciclib, the recommended dose of abemaciclib is 150 mg orally, twice daily. Abemaciclib may be taken with or without food. Refer to the Full Prescribing Information for abemaciclib.

When fulvestrant injection is used in combination with ribociclib, the recommended dose of ribociclib is 600mg taken orally, once daily for 21 consecutive days followed by 7 days off treatment resulting in a complete cycle of 28 days. Ribociclib can be taken with or without food. Refer to the Full Prescribing Information for ribociclib.

Pre/perimenopausal women treated with the combination of fulvestrant injection plus palbociclib, abemaciclib, or ribociclib, should be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to current clinical practice standards *[see Clinical Studies (14)]*.

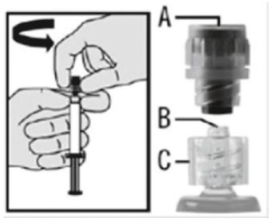
Dose Modification
Monotherapy
Hepatic Impairment:
A dose of 250 mg is recommended for patients with moderate hepatic impairment (Child-Pugh class B) to be administered intramuscularly into the buttock (gluteal area) slowly (1 to 2 minutes) as one 5 mL injection on Days 1, 15, 29, and once monthly thereafter. Fulvestrant injection has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C) *[see Warnings and Precautions (5.2)* and *Use in Specific Populations (8.6)]*.

Combination Therapy
When fulvestrant injection is used in combination with palbociclib, abemaciclib, or ribociclib, refer to monotherapy dose modification instructions for fulvestrant injection. Refer to the Full Prescribing Information of co-administered palbociclib, abemaciclib, or ribociclib for dose modification guidelines in the event of toxicities, for use with concomitant medications, and other relevant safety information.

Administration Technique
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 Warnings and Precautions (5.3)* and *Adverse Reactions (6.1)]*.

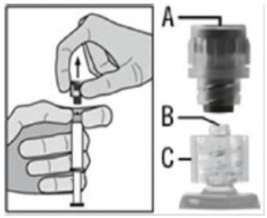
The proper method of administration of fulvestrant injection for intramuscular use is described in the following instructions. For each single-dose prefilled syringe:
1. Remove glass syringe barrel from tray and check that it is not damaged.
2. Remove perforated patient record label from syringe.
3. 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 TWIST THE CAP COUNTER-CLOCKWISE 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

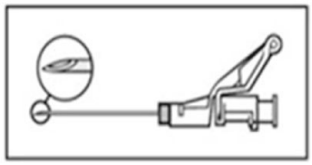


7. Attach the safety needle to the syringe tip (Luer-Lok). Twist needle until firmly seated (see Figure 3). Confirm that the needle is locked to the Luer connector before moving or tilting the syringe out of the vertical plane to avoid spillage of syringe contents.

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 to 2 minutes per 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 activate the lever arm to deploy the needle shielding by applying a single-finger stroke to the activation assisted lever arm to push the lever arm completely forward. Listen for a click. Confirm that the needle shielding has completely covered the needle (see Figure 5). NOTE: Activate away from self and others.

Figure 5

13. Discard the empty syringe into an approved sharps collector in accordance with applicable regulations and institutional policy.
14. Repeat steps 1 through 13 for second syringe.

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

SAFETYGLIDE™ INSTRUCTIONS FROM BECTON DICKINSON
SafetyGlide™ is a trademark of Becton Dickinson and Company.

Important Administration Information
To help avoid HIV (AIDS), HBV (Hepatitis), and other infectious diseases due to accidental needlesticks, contaminated needles should not be recapped or removed, unless there is no alternative or that such action is required by a specific medical procedure. Hands must remain behind the needle at all times during use and disposal. Do not autoclave SafetyGlide™ Needle before use. Becton Dickinson guarantees the contents of their unopened or undamaged packages to be sterile, non-toxic, and non-pyrogenic.

OVERDOSAGE

Human experience of overdose with fulvestrant is limited. There are isolated reports of overdose with fulvestrant in humans. No adverse reactions were seen in healthy male and female volunteers who received intravenous fulvestrant, which resulted in peak plasma concentrations at the end of the infusion, that were approximately 10 to 15 times those seen after intramuscular injection. The potential toxicity of fulvestrant at these or higher concentrations in cancer patients who may have additional comorbidities is unknown. There is no specific treatment in the event of fulvestrant overdose, and symptoms of overdose are not established. In the event of an overdose, healthcare practitioners should follow general supportive measures and should treat symptomatically.

INDICATIONS AND USAGE

Monotherapy
Fulvestrant injection is indicated for the treatment of:
- Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy, or
- HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.

Combination Therapy
Fulvestrant injection is indicated for the treatment of:
- HR-positive, HER2-negative advanced or metastatic breast cancer in postmenopausal women in combination with ribociclib as initial endocrine based therapy or following disease progression on endocrine therapy.
- HR-positive, HER2-negative advanced ormetastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.

HOW SUPPLIED/STORAGE AND HANDLING

Fulvestrant injection is supplied as two 5 mL clear neutral glass (Type 1) barrels, each containing 250 mg per 5 mL of sterile, clear, colorless to yellow, viscous fulvestrant injection solution for intramuscular injection and is NOT fitted with a tamper evident closure.

NDC 0143-9022-02

The single-dose prefilled syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlide™) for connection to the barrel.

Discard each syringe after use. If a patient dose requires only one syringe, unused syringe should be stored as directed below.

Storage:
REFRIGERATE, 2° TO 8°C (36° TO 46°F). TO PROTECT FROM LIGHT, STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE.

ENDING INFORMATION

Patient Counseling Information should be shared with the patient prior to administration.
For additional information, please refer to the Package Insert for full prescribing information, available on www.hikma.com.

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689 or FDA at 1-800 FDA-1088 or www.fda.gov/medwatch.

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