Press Release

Hikma launches Cefazolin for Injection, USP, in the US

London, 20 March 2023 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, announces it has launched Cefazolin for Injection, USP, in 2g and 3g doses. The drug, launched in the US, is used to treat certain infections caused by bacteria including skin, bone, joint, genital, blood, lining of heart chambers and heart valves, respiratory tract, biliary tract, and urinary tract infections and for perioperative prophylaxis[1].

Hikma is introducing the first 3g presentation to the US market and we are pleased to expand our portfolio with this launch, broadening the choice of medicines available to hospitals.

Hikma is a top three supplier of generic injectable medicines by volume in the US with a portfolio of over 130 products.[2]

- 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 North America, 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 8,800 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

[1] Refer to the safety information below for the full indication and usage
[2] IQVIA MAT December 2022, generic injectable volumes by eaches, excluding branded generics and Becton Dickinson

hikma.

This product has been approved for marketing in the United States by the US FDA. This product approval does not confer the right on Hikma, or any other party, to market this product outside the United States.

Important Safety Information for Cefazolin for Injection, USP, 2g and 3g:

CONTRAINDICATIONS

Cefazolin for Injection is contraindicated in patients who have a history of immediate hypersensitivity reactions (e.g., anaphylaxis, serious skin reactions) to cefazolin or the cephalosporin class of antibacterial drugs, penicillins, or other beta-lactams *[see Warnings and Precautions (5.1)].*

WARNINGS & PRECAUTIONS

- **Hypersensitivity Reactions to Cefazolin, Cephalosporins, Penicillins, or Other Beta-lactams -** Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterial drugs. Before therapy with Cefazolin for Injection is instituted, careful inquiry should be made to determine whether the patient has had previous immediate hypersensitivity reactions to cefazolin, cephalosporins, penicillins, or carbapenems. Exercise caution if this product is to be given to penicillin-sensitive patients because cross-hypersensitivity among beta-lactam antibacterial drugs has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to Cefazolin for Injection occurs, discontinue the drug.
- **Seizures in Patients with Renal Impairment -** Seizures may occur with the administration of Cefazolin for Injection, particularly in patients with renal impairment when the dosage is not reduced appropriately. Discontinue Cefazolin for Injection if seizures occur or make appropriate dosage adjustments in patients with renal impairment *[see Dosage and Administration]*. Anticonvulsant therapy should be continued in patients with known seizure disorders.
- ***Clostridioides difficile*-associated Diarrhea -** *Clostridioides difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including cefazolin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.
- **Risk of Development of Drug-resistant Bacteria -** Prescribing Cefazolin for Injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. Prolonged use of Cefazolin for Injection may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.
- **Prothrombin Activity -** Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.
- **Drug/Laboratory Test Interactions -** Urinary Glucose: A false positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution or with CLINITEST® tablets, but not with enzyme-based tests such as CLINISTIX®. Coombs Test: Positive direct and indirect antiglobulin (Coombs) tests have occurred; these may also occur in neonates whose mothers received cephalosporins before delivery.

ADVERSE REACTIONS

The following clinically significant adverse reactions to cefazolin for injection are described below and elsewhere in the labeling:

- Hypersensitivity reactions to Cefazolin, Cephalosporins, Penicillins, or Other Beta- lactams *[see Warnings and Precautions (5.1)]*
- Seizures in Patients with Renal Impairment *[see Warnings and Precautions (5.2)]*
- *Clostridioides difficile*-associated Diarrhea *[see Warnings and Precautions (5.3)]*

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The following reactions have been reported:

Gastrointestinal: Diarrhea, oral candidiasis (oral thrush), vomiting, nausea, stomach cramps, anorexia and *Clostridioides difficile* colitis. Onset of *Clostridioides difficile* colitis symptoms may occur during or after antibacterial treatment *[see Warnings and Precautions (5.3)].*
Allergic: Anaphylaxis, eosinophilia, itching, drug fever, skin rash, Stevens-Johnson syndrome.
Hematologic: Neutropenia, leukopenia, thrombocytopenia, thrombocythemia.
Hepatic: Transient rise in serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase levels has been observed. Reports of hepatitis have been received.
Renal: Reports of increased BUN and creatinine levels, as well as renal failure, have been received.
Local Reactions: Instances of phlebitis have been reported at site of injection. Some induration has occurred.
Other Reactions: Pruritus (including genital, vulvar and anal pruritus, genital moniliasis, and vaginitis).

Postmarketing Experience
The following adverse reactions have been identified during post approval use of cefazolin. 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.

Immune system disorders: Serum sickness-like reaction
Renal and urinary disorders: Acute tubulointerstitial nephritis (ATIN)
Skin and subcutaneous tissue disorders: Acute generalized exanthematous pustulosis (AGEP)

Cephalosporin-class Adverse Reactions
In addition to the adverse reactions listed above that have been observed in patients treated with cefazolin, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibacterials:

Erythema multiforme, toxic epidermal necrolysis, renal impairment, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic impairment including cholestasis, and pancytopenia.

DRUG INTERACTIONS

The renal excretion of cefazolin is inhibited by probenecid. Co-administration of probenecid with Cefazolin for Injection is not recommended.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
Available data from published prospective cohort studies, case series and case reports over several decades with cefazolin use in pregnant women have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. These studies have methodologic limitations, including small sample size, retrospective study design, and inconsistent comparator groups. Cefazolin crosses the placenta.

Lactation
Risk Summary
Data from published literature report that cefazolin is present in human milk but is not expected to accumulate in a breastfed infant. There are no data on the effects of cefazolin on the breastfed child or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Cefazolin for Injection and any potential adverse effects on the breastfed child from Cefazolin for Injection or from the underlying maternal condition.

Pediatric Use
Cefazolin for Injection is indicated for the treatment of respiratory tract infections, urinary tract infections, skin and skin structure infections, biliary tract infections, bone and joint infections, genital infections, septicemia, and endocarditis in pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved *[see Indications and Usage (1.1 to 1.8) and Dosage and Administration (2.2)]*.

Safety and effectiveness of Cefazolin for Injection in premature infants and neonates have not been established.

Geriatric Use
Of the 920 subjects who received cefazolin for injection in clinical studies, 313 (34%) were 65 years and over, while 138 (15%) were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Dosage and Administration (2.5) and Warnings and Precautions (5.2)]*.

Renal Impairment
When Cefazolin for Injection is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required *[see Dosage and Administration (2.5)]*.

DOSAGE AND ADMINISTRATION

Important Administration Instructions
Administer Cefazolin for Injection by Intravenous Infusion only. **Not** for Intravenous bolus administration or Intramuscular administration.

Dosage for the Treatment of Infections
Dosage for the Treatment of Infections in Adults with Creatinine Clearance (CLcr) Equal to 55 mL/min or Greater
The recommended adult dosages of Cefazolin for Injection for the treatment of infections *[see Indications and Usage (1.1 to 1.8)]* are outlined in Table 1 in the package insert. Administer Cefazolin for Injection by intravenous infusion *[see Dosage and Administration (2.6)]*.

Dosage for the Treatment of Infections in Pediatric Patients 1 Month of Age and Older with CLcr Equal to 70 mL/min or Greater
The recommended pediatric dosages for the treatment of infections *[see Indications and Usage (1.1 to 1.8)]* are outlined in Table 2 in the package insert. Administer Cefazolin for Injection by Intravenous Infusion *[see Dosage and Administration (2.6)]*.

Dosage for Perioperative Prophylactic Use in Adults
Dosage for Perioperative Prophylaxis in Adults with CLcr Equal to 55 mL/min or Greater
To prevent postoperative infection in contaminated or potentially contaminated surgery, recommended dosages are described in Table 3 in the package insert. Administer Cefazolin for Injection by Intravenous Infusion. **Not** for Intravenous bolus administration or Intramuscular administration *[see Dosage and Administration (2.5, 2.6)]*.

It is important that (1) the preoperative dose be given just (1/2 hour to 1 hour) prior to the start of surgery so that adequate antibacterial levels are present in the serum and tissues at the time of initial surgical incision; and (2) Cefazolin for Injection be administered, if necessary, at appropriate intervals during surgery to provide sufficient levels of the antibacterial drug at the anticipated moments of greatest exposure to infective organisms.

The perioperative prophylactic administration of cefazolin should usually be discontinued within a 24-hour period after the surgical procedure. In surgery where the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of Cefazolin for Injection may be continued for 3 to 5 days following the completion of surgery.

Pediatric Dosage Preparation Guide
Refer to Table 4 in the package insert for Pediatric Dosage Guide 25 mg/kg/day Divided into 3 Doses. Refer to Table 5 in the package insert for Pediatric Dosage Guide 25 mg/kg/day Divided into 4 Doses. Refer to Table 6 in the package insert for Pediatric Dosage Guide 50 mg/kg/day Divided into 3 Doses. Refer to Table 7 in the package insert for Pediatric Dosage Guide 50 mg/kg/day Divided into 4 Doses.

Dosage Recommendations in Adult and Pediatric Patients with Renal Impairment
Dosage Recommendations in Adult Patients with CLcr less than 55 mL/min

The dosage recommendation of Cefazolin for Injection in adult patients with renal impairment (CLcr less than 55 mL/min) is outlined in Table 8 in the package insert.

Dosage Recommendations in Pediatric Patients 1 Month of Age and Older with CLcr less than 70 mL/min
The dosage recommendation of Cefazolin for Injection in pediatric patients 1 month of age and older with renal impairment (CLcr less than 70 mL/min) is outlined in Table 9 in the package insert.

Preparation of Cefazolin for Injection
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter is evident in reconstituted fluids, the drug solutions should be discarded. Reconstituted solutions may range in color from pale yellow to yellow.

Reconstitution and Dilution
For intravenous infusion, reconstitute Cefazolin for Injection single-dose vials with Sterile Water for Injection according to Table 10 in the package insert and *shake well*. After reconstitution further dilute according to Table 10 using the following diluents:

For intermittent or continuous infusion: Dilute reconstituted Cefazolin for Injection in one of the following solutions:
• Sodium Chloride Injection, USP
• 5% Dextrose Injection, USP

Discard unused portion.

Storage of Reconstituted and Diluted Solutions
When reconstituted or diluted according to the instructions above, Cefazolin for Injection is stable for 24 hours at room temperature or for 7 days if stored under refrigeration at 2°C to 8°C (36°F to 46°F).

OVERDOSAGE

Accidental overdosage resulting in seizures may occur in patients with renal impairment who receive doses greater than the recommended dosage of Cefazolin for Injection *[see Warnings and Precautions (5.2)]*. If seizures associated with accidental overdosage occur, discontinue Cefazolin for Injection and give supportive treatment.

INDICATIONS AND USAGE

Respiratory Tract Infections
Cefazolin for Injection is indicated for the treatment of respiratory tract infections due to *Streptococcus pneumoniae, Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (methicillin-susceptible), and Group A beta-hemolytic streptococci in adults and pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved *[see Dosage and Administration (2.1, 2.2, 2.4 and 2.5)].*

Limitations of Use
Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cefazolin for Injection is indicated for the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of Cefazolin for Injection in the subsequent prevention of rheumatic fever are not available at present.

Urinary Tract Infections
Cefazolin for Injection is indicated for the treatment of urinary tract infections due to *Escherichia coli, Proteus mirabilis,* and *Klebsiella* species (spp.) in adults and pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved *[see Dosage and Administration (2.1, 2.2, 2.4 and 2.5)].*

Skin and Skin Structure Infections
Cefazolin for Injection is indicated for the treatment of skin and skin structure infections due to *S. aureus* (methicillin-susceptible), Group A beta-hemolytic streptococci, and *Streptococcus* species (spp.) in adults and pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved *[see Dosage and Administration (2.1, 2.2, 2.4 and 2.5)].*

Biliary Tract Infections
Cefazolin for Injection is indicated for the treatment of biliary tract infections due to *E. coli,* various isolates of *Streptococcus* spp., *P. mirabilis, Klebsiella* spp., and *S. aureus* (methicillin-susceptible*)* in adults and pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved *[see Dosage and Administration (2.1, 2.2, 2.4 and 2.5)].*

Bone and Joint Infections
Cefazolin for Injection is indicated for the treatment of bone and joint infections due to *S. aureus* in adults and pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved *[see Dosage and Administration (2.1, 2.2, 2.4 and 2.5)].*

Genital Infections
Cefazolin for Injection is indicated for the treatment of genital infections (i.e., prostatitis, epididymitis) due to *E. coli, P. mirabilis,* and *Klebsiella* species in adults and pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved *[see Dosage and Administration (2.1, 2.2, 2.4 and 2.5)].*

Septicemia
Cefazolin for Injection is indicated for the treatment of septicemia due to *S. pneumoniae, S. aureus* (methicillin-susceptible), *P. mirabilis, E. coli,* and *Klebsiella* species in adults and pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved *[see Dosage and Administration (2.1, 2.2, 2.4 and 2.5)].*

Endocarditis
Cefazolin for Injection is indicated for the treatment of endocarditis due to *S. aureus* (methicillin-susceptible) and Group A beta-hemolytic streptococci in adults and pediatric patients 1 month of age and older for whom appropriate dosing with this formulation can be achieved *[see Dosage and Administration (2.1, 2.2, 2.4 and 2.5)].*

Perioperative Prophylaxis
Cefazolin for Injection is indicated for perioperative prophylaxis in adults. The prophylactic administration of Cefazolin for Injection preoperatively, intraoperatively and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures which are classified as contaminated or potentially contaminated (e.g., vaginal hysterectomy, and cholecystectomy in high-risk patients such as those older than 70 years, with acute cholecystitis, obstructive jaundice, or common duct bile stones).

The perioperative use of Cefazolin for Injection is indicated in surgical patients in whom infection at the operative site would present a serious risk (e.g., during open-heart surgery and prosthetic arthroplasty).

The prophylactic administration of Cefazolin for Injection should usually be discontinued within a 24-hour period after the surgical procedure. In surgery where the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of Cefazolin for Injection may be continued for 3 to 5 days following the completion of surgery.

If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism so that appropriate therapy may be instituted *[see Dosage and Administration (2.3)]*.

Usage
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefazolin for Injection and other antibacterial drugs, Cefazolin for Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

HOW SUPPLIED/STORAGE AND HANDLING

Cefazolin for Injection is available as 2 grams or 3 grams of cefazolin as a white to off-white crystalline powder in single-dose vial for reconstitution.

Cefazolin for Injection, USP	Packaged	NDC No.
2 grams/vial	Carton of 25 vials	0143-9139-25
3 grams/vial	Carton of 25 vials	0143-9140-25

Before reconstitution protect from light and store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Storage conditions for reconstituted and diluted solutions of Cefazolin for Injection are described in another section of labeling *[see Dosage and Administration (2.6)].*

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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