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Press Release

Hikma launches Doxycycline for Injection

London, 25 June 2021 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Doxycycline for Injection, USP, 100mg, in the US, through its US affiliate, Hikma Pharmaceuticals USA Inc.

Doxycycline for Injection is an antibiotic indicated to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. It is used to treat various bacterial infections, including pneumonia and other respiratory tract infections.

According to IQVIA, US sales of Doxycycline for Injection, USP, 100mg, were approximately $43 million in the 12 months ending April 2021.

Hikma is the third largest US supplier of generic injectable medicines by volume, with a growing portfolio of over 100 products. Today one in every six injectable generic medicines used in US hospitals is a Hikma product.

- 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 8,600 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 Doxycycline for Injection, USP, 100mg:

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS & PRECAUTIONS

- The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported.
- *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including doxycycline for injection, USP, and may range in severity from mild diarrhea to fatal colitis.
- *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains 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 antibiotic use.
- Severe skin reactions, such as exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients receiving doxycycline.
- Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracyclines including doxycycline. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline associated IH. Concomitant use of isotretinoin and doxycycline should be avoided because isotretinoin is also known to cause pseudotumor cerebri. Although IH typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists.
- Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines.
- The anti-anabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.
- As with other antibacterial drugs, use of doxycycline may result in overgrowth of nonsusceptible organisms, including fungi.
- Incision and drainage or other surgical procedures should be performed in conjunction with antibacterial therapy, when indicated.
- Prescribing doxycycline in the absence of 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.
- All infections due to group A beta-hemolytic streptococci should be treated for at least 10 days.
- Patients taking doxycycline should be advised:
    - To avoid excessive sunlight or artificial ultraviolet light while receiving doxycycline and to discontinue therapy if phototoxicity (e.g., skin eruption, etc.) occurs. Sunscreen or sunblock should be considered.
    - That the use of doxycycline might increase the incidence of vaginal candidiasis.
- Patients should be counseled that antibacterial drugs, including doxycycline should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When doxycycline is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed.

Laboratory Tests:

- In venereal diseases when coexistent syphilis is suspected, a dark field examination should be done before treatment is started and the blood serology repeated monthly for at least 4 months. In long-term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal, and hepatic studies should be performed.
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General Precaution

As with other antibacterial drugs, use of doxycycline may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, doxycycline should be discontinued and appropriate therapy instituted.

ADVERSE REACTIONS

Gastrointestinal
Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis and inflammatory lesions (with monilial overgrowth) in the anogenital region, and pancreatitis. Hepatotoxicity has been reported rarely. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Superficial discoloration of the adult permanent dentition, reversible upon drug discontinuation and professional dental cleaning has been reported. Permanent tooth discoloration and enamel hypoplasia may occur with drugs of the tetracycline class when used during tooth development.

Skin
Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above.

Renal Toxicity
Rise in BUN has been reported and is apparently dose related.

Immune
Hypersensitivity reactions including urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis and exacerbation of systemic lupus erythematosus, drug reaction with eosinophilia and systemic symptoms (DRESS).

Other
Bulging fontanels in infants and intracranial hypertension in adults.

Blood
Hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported.

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur.

DRUG INTERACTIONS

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline in conjunction with penicillin.

Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

The concurrent use of tetracycline and Penthrane ® (methoxyflurane) has been reported to result in fatal renal toxicity.

Concurrent use of tetracycline may render oral contraceptives less effective.

USE IN SPECIFIC POPULATIONS

Usage in Pregnancy
Doxycycline for Injection has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient.

Results of animal studies indicate that tetracycline cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development).

Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

Usage in Children
The use of Doxycycline for Injection in children under 8 years is not recommended because safe conditions for its use have not been established. Because of the effects of drugs of the tetracycline-class on tooth development and growth, use of doxycycline in pediatric patients 8 years of age or less only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g., anthrax, Rocky Mountain spotted fever), particularly when there are no alternative therapies.

As with other tetracyclines, doxycycline forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

DOSAGE AND ADMINISTRATION

NOTE: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not indicated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

The usual dosage and frequency of administration of Doxycycline for Injection (100 to 200 mg/day) differs from that of the other tetracyclines (1 to 2 g/day). Exceeding the recommended dosage may result in an increased incidence of side effects.

Studies to date have indicated that doxycycline hyclate at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Adults
The usual dosage of doxycycline for injection is 200 mg on the first day of treatment administered in one or two infusions. Subsequent daily dosage is 100 to 200 mg depending upon the severity of infection, with 200 mg administered in one or two infusions.

In the treatment of primary and secondary syphilis, the recommended dosage is 300 mg daily for at least 10 days.

In the treatment of inhalational anthrax (post-exposure) the recommended dose is 100 mg of doxycycline, twice a day. Parenteral therapy is only indicated when oral therapy is not indicated and should not be continued over a prolonged period of time. Oral therapy should be instituted as soon as possible. Therapy must continue for a total of 60 days.

Pediatric Patients
For all pediatric patients weighing less than 45 kg with severe or life-threatening infections (e.g., anthrax, Rocky Mountain spotted fever), the recommended dosage is 2.2 mg/kg of body weight administered every 12 hours. Children weighing 45 kg or more should receive the adult dose.

For pediatric patients with less severe disease (greater than 8 years of age and weighing less than 45 kg), the recommended dosage schedule is 4.4 mg/kg of body weight divided into two doses on the first day of treatment, followed by a maintenance dose of 2.2 mg/kg of body weight (given as a single daily dose or divided into twice daily doses). For pediatric patients weighing over 45 kg, the usual adult dose should be used.

In the treatment of inhalational anthrax (post-exposure) the recommended dose is 2.2 mg/kg of body weight, twice a day in children weighing less than 45 kg. Parenteral therapy is only indicated when oral therapy is not indicated and should not be continued over a prolonged period of time. Oral therapy should be instituted as soon as possible. Therapy must continue for a total of 60 days.

General
The duration of infusion may vary with the dose (100 to 200 mg/day), but is usually one to four hours. A recommended minimum infusion time for 100 mg of a 0.5 mg/mL solution is one hour. Therapy should be continued for at least 24 to 48 hours after symptoms and fever have subsided. The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

Intravenous solutions should not be injected intramuscularly or subcutaneously. Caution should be taken to avoid the inadvertent introduction of the intravenous solution into the adjacent soft tissue.

PREPARATION OF SOLUTION
To prepare a solution containing 10 mg/mL, the contents of the vial should be reconstituted with 10 mL (for the 100 mg/vial container) of Sterile Water for Injection or any of the 10 intravenous infusion solutions listed below. Each 100 mg of doxycycline for injection (i.e., withdraw entire solution from the 100 mg vial) is further diluted with 100 mL to 1,000 mL of the intravenous solutions listed below:

1. Sodium Chloride Injection, USP
2. 5% Dextrose Injection, USP
3. Ringer's Injection, USP
4. Invert Sugar, 10% in Water
5. Lactated Ringer's Injection, USP
6. Dextrose 5% in Lactated Ringer's
7. Normosol-M ® in D5-W
8. Normosol-R ® in D5-W
9. Plasma-Lyte ® 56 in 5% Dextrose
10. Plasma-Lyte ® 148 in 5% Dextrose

This will result in desired concentrations of 0.1 to 1 mg/mL. Concentrations lower than 0.1 mg/mL or higher than 1 mg/mL are not recommended.

Stability
Doxycycline is stable for 48 hours in solution when diluted with Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, to concentrations between 1 mg/mL and 0.1 mg/mL and stored at 25°C. Doxycycline in these solutions is stable under fluorescent light for 48 hours, but must be protected from direct sunlight during storage and infusion. Reconstituted solutions (1 to 0.1 mg/mL) may be stored up to 72 hours prior to start of infusion if refrigerated and protected from sunlight and artificial light. Infusion must then be completed within 12 hours. Solutions must be used within these time periods or discarded.

Doxycycline, when diluted with Ringer's Injection, USP, or Invert Sugar, 10% in Water, to a concentration between 1 mg/mL and 0.1 mg/mL, must be completely infused within 12 hours after reconstitution to ensure adequate stability. During infusion, the solution must be protected from direct sunlight. Reconstituted solutions (1 to 0.1 mg/mL) may be stored up to 72 hours prior to start of infusion if refrigerated and protected from sunlight and artificial light. Infusion must then be completed within 12 hours. Solutions must be used within these time periods or discarded.

Diluted solutions (0.1 to 1 mg/mL) prepared using Normosol-M ® in D5-W; Normosol-R ® in D5-W; Plasma-Lyte ® 56 in 5% Dextrose; or Plasma-Lyte ® 148 in 5% Dextrose may also be stored up to 12 hours prior to start of infusion, if refrigerated and protected from sunlight and artificial light. The infusion must be completed within 12 hours. Solutions must be used within these time periods or discarded.

When diluted with Lactated Ringer's Injection, USP, or Dextrose 5% in Lactated Ringer's, infusion of the solution (ca. 1 mg/mL) or lower concentrations (not less than 0.1 mg/mL) must be completed within six hours after reconstitution to ensure adequate stability. During infusion, the solution must be protected from direct sunlight. Solutions must be used within this time period or discarded.

Solutions of doxycycline for injection, at a concentration of 10 mg/mL in Sterile Water for Injection, when frozen immediately after reconstitution are stable for eight weeks when stored at –20°C. If the product is warmed, care should be taken to avoid heating it after the thawing is complete. Once thawed the solution should not be refrozen.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Doxycycline for Injection, USP and other antibacterial drugs, Doxycycline for Injection, USP 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.

Doxycycline for Injection, USP is indicated in infections caused by the following microorganisms:

- Rickettsiae (Rocky Mountain spotted fever, typhus fever, and the typhus group, Q fever, rickettsial pox and tick fevers).
- *Mycoplasma pneumoniae* (PPLO, Eaton Agent).
- Agents of psittacosis and ornithosis.
- Agents of lymphogranuloma venereum and granuloma inguinale.
- The spirochetal agent of relapsing fever *(Borrelia recurrentis)*.

The following gram-negative microorganisms:

- *Haemophilus ducreyi* (chancroid).
- *Yersinia pestis* (formerly *Pasteurella pestis*) and *Francisella tularensis* (formerly *Pasteurella tularensis*).
- *Bartonella bacilliformis*.
- *Bacteroides* species.
- *Vibrio cholerae* (formerly *Vibrio comma*) and *Campylobacter fetus* (formerly *Vibrio fetus*).
- *Brucella* species (in conjunction with streptomycin).

Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended.

Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

- *Escherichia coli*.
- *Enterobacter aerogenes* (formerly *Aerobacter aerogenes*).
- *Shigella* species.
- *Acinetobacter* species (formerly *Mima* species and *Herellea* species).
- *Haemophilus influenzae* (respiratory infections).
- *Klebsiella* species (respiratory and urinary infections).

Doxycycline is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

- *Streptococcus* species:

Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Enterococcus faecalis* (formerly *Streptococcus faecalis*) have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organism has been demonstrated to be sensitive.

For upper respiratory infections due to group A beta-hemolytic streptococci, penicillin is the usual drug of choice, including prophylaxis of rheumatic fever.

- *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*).
- *Staphylococcus aureus*, respiratory, skin and soft tissue infections. Tetracyclines are not the drugs of choice in the treatment of any type of staphylococcal infections.
- Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.

When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of infections due to:

- *Neisseria gonorrhoeae* and *N. meningitidis*.
- *Treponema pallidum* and *Treponema pertenue* (syphilis and yaws).
- *Listeria monocytogenes*.
- *Clostridium* species.
- *Fusobacterium fusiforme* (Vincent's infection).
- *Actinomyces* species.

In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides.

Plasmodium falciparum:

Doxycycline has been found to be active against the asexual erythrocytic forms of Plasmodium falciparum but not against the gametocytes of P. falciparum. The precise mechanism of action of the drug is not known.

Doxycycline is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence.

ENDING INFORMATION

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 the FDA at 1-800-FDA-1088 or **www.fda.gov/medwatch**. For Product Inquiry call 1-877-845-0689.

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