נובמבר 2020

רופא/ה יקר/ה,
רוקח/ת יקר/ה,

הנדון: קיוביצין 500 מ"ג - CUBICIN® 500 mg

Dosage form: lyophilized powder for solution for injection
Composition: Daptomycin 500 mg/vial

חברת מרק שארפ ודוהם (ישראל-1996) בע"מ, (MSD ישראל), מבקשת ליידע על עדכון העלון לרופא של התכשיר CUBICIN 500mg.

להלן לשון ההתוויה המאושרת לתכשיר:
Cubicin is indicated for the treatment of the infections listed below.

- Complicated Skin and Skin Structure Infections

Complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Grampositive bacteria: Staphylococcus aureus (including methicillin-resistant isolates), Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae subsp. equisimilis, and Enterococcus faecalis (vancomycin-susceptible isolates only).

- Staphylococcus aureus Bloodstream Infections (Bacteremia), Including Those with Right-Sided Infective Endocarditis, Caused by Methicillin-Susceptible and Methicillin-Resistant Isolates

Staphylococcus aureus bloodstream infections (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates.

Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram negative or anaerobic organisms

למידע מלא ולהוראות מתן מפורטות, יש לעיין בעלון לרופא המאושר על ידי משרד הבריאות.

עדכונים מהותיים שבוצעו בעלון לרופא:
טקסט שהוסף מודגש בקו תחתון, טקסט שנמחק מסומן בקו חוצה.

5 WARNINGS AND PRECAUTIONS

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5.3 Eosinophilic Pneumonia

Eosinophilic pneumonia has been reported in patients receiving **CUBICIN** [see Adverse Reactions (6.2)]. In reported cases associated with **CUBICIN**, patients developed fever, dyspnea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates or organizing pneumonia. In general, patients developed eosinophilic pneumonia 2 to 4 weeks after starting **CUBICIN** and improved when **CUBICIN** was discontinued and steroid therapy was initiated. Recurrence of eosinophilic pneumonia upon re-exposure has been reported. Patients who develop these signs and symptoms while receiving **CUBICIN** should undergo prompt medical evaluation, and **CUBICIN** should be discontinued immediately. Treatment with systemic steroids is recommended.

5.4 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

DRESS has been reported in post-marketing experience with **CUBICIN** *[see Adverse Reactions (6.2)].* Patients who develop skin rash, fever, peripheral eosinophilia, and systemic organ (for example, hepatic, renal, pulmonary) impairment while receiving **CUBICIN** should undergo medical evaluation. If DRESS is suspected, discontinue **CUBICIN** promptly and institute appropriate treatment.

MSD

5.5 Tubulointerstitial Nephritis (TIN)

TIN has been reported in post-marketing experience with **CUBICIN** *[see Adverse Reactions (6.2)].* Patients who develop new or worsening renal impairment while receiving **CUBICIN** should undergo medical evaluation. If TIN is suspected, discontinue **CUBICIN** promptly and institute appropriate treatment.

5.6 Peripheral Neuropathy

Cases of peripheral neuropathy have been reported during the **CUBICIN** postmarketing experience *[see Adverse Reactions (6.2)]*. Therefore, physicians should be alert to signs and symptoms of peripheral neuropathy in patients receiving **CUBICIN**. Monitor for neuropathy and consider discontinuation.

6 ADVERSE REACTIONS

The following adverse reactions are described, or described in greater detail, in other sections:

- Anaphylaxis/hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- Myopathy and rhabdomyolysis *[see Warnings and Precautions (5.2)]*
- Eosinophilic pneumonia *[see Warnings and Precautions (5.3)]*
- Drug reaction with eosinophilia and systemic symptoms *[see Warnings and Precautions (5.4)]*
- Tubulointerstitial nephritis *[see Warnings and Precautions (5.5.)]*
- Peripheral neuropathy *[see Warnings and Precautions (5.46)]*
- Increased International Normalized Ratio (INR)/prolonged prothrombin time *[see Warnings and Precautions (5.11) and Drug Interactions (7.2)]*

6.2 Post-Marketing Experience

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Blood and lymphatic system disorders: anemia, thrombocytopenia

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Immune System Disorders: anaphylaxis; hypersensitivity reactions, including angioedema, ~~drug rash with eosinophilia and systemic symptoms (DRESS),~~ pruritus, hives, shortness of breath, difficulty swallowing, truncal erythema, and pulmonary eosinophilia *[see Contraindications (4), Warnings and Precautions (5.1)]*

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Laboratory Investigations: platelet count decreased

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Respiratory, Thoracic, and Mediastinal Disorders: cough, eosinophilic pneumonia, organizing pneumonia *[see Warnings and Precautions (5.3)]*

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Skin and Subcutaneous Tissue Disorders: serious skin reactions, including drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome and vesiculobullous rash (with or without mucous membrane involvement), acute generalized exanthematous pustulosis *[see Warnings and Precautions (5.4)].*

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Renal and urinary disorders: acute kidney injury, renal insufficiency, ~~and~~ renal failure, and tubulointerstitial nephritis (TIN) *[see Warnings and Precautions (5.5)].*

8.1 Pregnancy

~~Teratogenic Effects: Pregnancy Category B~~
Risk Summary

Limited published data on use~~There are no adequate and well-controlled trials~~ of **CUBICIN** in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies~~. Embryofetal development studies~~ performed in rats

and rabbits daptomycin was administered intravenously during organogenesis at doses ~~of up to 75 mg/kg (~~2 and 4 times, respectively, the recommended 6 mg/kg human dose~~, respectively,~~ (on a body surface area basis). ~~revealed n~~No evidence of adverse developmental outcomes was observed.

~~harm to the fetus due to daptomycin. Because animal reproduction studies are not always predictive of human response, **CUBICIN** should be used during pregnancy only if the potential benefit outweighs the possible risk.~~

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In pregnant rats, daptomycin was administered intravenously at doses of 5, 20, or 75 mg/kg/day during the gestation days 6 to 18. Maternal body weight gain was decreased at 75 mg/kg/day. No embryo/fetal effects were noted at the highest dose of 75 mg/kg/day, a dose approximately 2-fold higher than in humans at the recommended maximum dose of 6mg/kg (based on body surface area).

In pregnant rabbits, daptomycin was administered intravenously at doses of 5, 20, or 75 mg/kg/day during the gestation days 6 to 15. Maternal body weight gain and food consumption were decreased at 75 mg/kg/day. No embryo/fetal effects were noted at the highest dose of 75 mg/kg/day, a dose approximately 4-fold higher than in humans at the maximum recommended dose of 6mg/kg (based on body surface area).

In a combined fertility and pre/postnatal development study, daptomycin was administered intravenously to female rats at doses of 2, 25, 75 mg/kg/day from 14-days pre-mating through lactation/postpartum day 20). No effects on pre/postnatal development were observed up to the highest dose of 75 mg/kg/day, a dose approximately 2-fold higher than the maximum recommended human dose of 6 mg/kg (based on body surface area)[1].

8.3~~2~~ ~~Nursing Mothers~~Lactation

Risk Summary

Limited published data report that daptomycin is present in human milk at infant doses of 0.1% of the maternal dose *[see Data]*[2,3,4]. There is no information on the effects of daptomycin on the breastfed infant or the effects of daptomycin on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for **CUBICIN** and any potential adverse effects on the breastfed infant from **CUBICIN** or from the underlying maternal condition.

~~Daptomycin is present in human milk but is poorly bioavailable orally. In a single case study, **CUBICIN** was administered daily for 28 days to a nursing mother at an IV dose of 6.7 mg/kg/day, and samples of the patient's breast milk were collected over a 24-hour period on day 27. The highest measured concentration of daptomycin in the breast milk was 0.045 mcg/mL[4]. The calculated maximum daily **CUBICIN** dose to the infant (assuming mean milk consumption of 150 mL/kg/day) was 0.1% of the maternal dose of 6.7 mg/kg/day [see *Nonclinical Toxicology (13.2)*]. Caution should be exercised when **CUBICIN** is administered to a nursing woman.~~

8.4 Pediatric Use

~~Safety and effectiveness of **CUBICIN** in pediatric patients have not been established. Avoid use of **CUBICIN** in pediatric patients younger than 12 months due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) observed in neonatal dogs *[see Warnings and Precautions (5.5) and Nonclinical Toxicology (13.2)]*.~~

CUBICIN is not indicated for children and adolescents under 18 years of age.

12.3 Pharmacokinetics

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~~*Pediatric*~~

~~The pharmacokinetics of daptomycin in pediatric populations (<18 years of age) have not been established *[see Nonclinical Toxicology (13.2)].*~~

בעלון לרופא היו עדכונים נוספים שאינם מהותיים ואינם נכללים בהודעה זו. העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס על ידי פניה לבעל הרישום, חברת MSD ישראל, בטלפון 09-9533333.

CUBICIN 500mg מופץ ע"י חברת נובולוג בע"מ.

בברכה,

אורית בילין
רוקחת ממונה
MSD ישראל

Refrences:
Cubicin 500mg SPC 11/2020