***תאריך: פברואר 2021***

**רופא/ה, רוקח/ת נכבד/ה**

**חברת טבע מודיעה על העדכונים הבאים בעלון לרופא של התכשיר:**

# PENIBRIN® 500 mg
# PENIBRIN® 1 g
# PENIBRIN® 2 g
# Powder for Solution for Injection/Infusion

# פניברין® 500 מ"ג, פניברין® 1 גר', פניברין® 2 גר',
# אבקה להכנת תמיסה להזרקה/עירוי

**Contains: Ampicillin (as sodium salt) 500 mg, 1 g, 2 g**

## עדכונים בעלון לרופא

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**<u>התוויה כפי שאושרה בתעודת הרישום:</u>**

Penibrin injection is recommended in serious infections when prompt, effective levels of the antibiotic must reach the site of infection. Such infections include meningitis, subacute bacterial endocarditis, peritonitis, septicemia, severe forms of chronic bronchitis, osteomyelitis, pneumonia and pyelonephritis due to susceptible organisms.

**<u>ברצוננו להודיע שהעלון לרופא עודכן, בפירוט שלהלן כלולים העדכונים העיקריים בלבד (תוספות מסומנות באדום והסרות מידע כטקסט מחוק):</u>**

## 2. <u>לפני השימוש בתרופה</u>

### 4.4 Special warnings and precautions for use

Ampicillin has a limited spectrum of antibacterial activity. It is not suitable for use as a single agent for the treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a very high suspicion that the most likely pathogen(s) would be suitable for treatment with ampicillin. This particularly applies when considering the treatment of patients with intraabdominal infections, female genital infections and endocarditis. Ampicillin should be used in the treatment of cystitis only when susceptibility is documented.

Hypersensitivity and serum sickness-like reactions can be controlled with antihistamines and, if necessary, with systemic corticosteroids. If these types of reactions occur, ampicillin should be discontinued unless the doctor considers that the condition is life-threatening and can only be treated with ampicillin. Serious anaphylactic reactions require emergency

treatment with adrenalin, oxygen and intravenous steroids.

Antibiotic-associated colitis (caused in most cases by Clostridium difficile) has been reported with nearly all antibacterial agents including ampicillin and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients presenting diarrhoea during or after the administration of any antibiotic (cases have been reported up to two months after the administration of antibacterial medicinal products). Should antibiotic-associated colitis occur, ampicillin should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic drugs are contra-indicated in this

**[...]**

## 4.8 Undesirable effects

Summary of the safety profile

The most commonly reported undesirable effects are skin reactions (pruritis, rash, exanthema, itching), abdominal pain, meteorism, soft stools, diarrhoea, nausea and vomiting.

People who have previously experienced hypersensitivity to penicillin and people with allergy, asthma, hay fever or urticaria in their medical history have a greater risk of hypersensitivity reactions.

| **System Organ Class** | **Preferred Term** |
|---|---|
| Infections and infestations | |
| Uncommon | Infection with fungi or resistant bacteria especially during prolonged and/or repeated use |
| Blood and lymphatic system disorders | |
| Uncommon | Thrombocytopenia, anaemia, agranulocytosis, leukopenia, eosinophilia, thrombocytopenic purpura, haemolytic anaemia. |
| Very rare | Granulocytopenia, pancytopenia, prolongation of bleeding and prothrombin time[1]. |
| Immune system disorders [2,8] | |
| Uncommon | Serious allergic reactions such as serum sickness, allergic nephritis. |
| Rare | Life-threatening anaphylactic shock[6]. |
| Not known | Hypersensitivity (see section 4.4) |
| Nervous system disorders[9] | |
| Rare | Dizziness, headache, myoclonus and seizures (in renal insufficiency or at very high intravenous doses). |
| Respiratory, thoracic and mediastinal disorders | |
| Uncommon | Laryngeal oedema |
| Gastrointestinal disorders | |

| | |
|---|---|
| Very common | Abdominal pain, nausea, vomiting, meteorism, soft stools, diarrhoea[7]. |
| Uncommon | Enterocolitis, stomatitis, glossitis, pseudomembranous colitis[8] (in most cases caused by Clostridium difficile) |
| Not known | Black hairy tongue |
| Skin and subcutaneous tissue disorders | |
| Very common | Pruritus, rash, exanthema, itching[3] |
| Common | Morbilliform rash[4], exanthema and enanthem in the oral region[5] |
| Uncommon | Angioneurotic oedema, allergic vasculitis, exfoliative dermatitis, exudative erythema multiforme, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis |
| Hepatobiliary disorders | |
| Uncommon | Transaminase elevation. |
| Musculoskeletal and connective tissue disorders | |
| Not known | Arthralgia |
| Renal and urinary disorders | |
| Uncommon | Crystalluria on high-dose intravenous administration, acute interstitial nephritis |
| Very Rare | Acute renal failure with excretion of urine crystals. |
| General disorders and administration site conditions | |
| Common | Swelling and pain, localised phlebitis. |
| Uncommon | Drug fever |
| Not known | Fever |

[1] See section 4.4.
[2] See sections 4.3 and 4.4.
[3] An immediate-type urticarial reaction generally suggests a true penicillin allergy and necessitates the interruption of treatment and institution of suitable medical measures. Medical advice should be sought regarding the future use of beta-lactam antibiotics.
[4] The typical, measles-like rash develops several (5 to 11) days after the start of treatment.
[5] The incidence of exanthem is higher in patients with infectious mononucleosis or lymphatic leukaemia.
[6] Allergic reactions are more likely to occur in patients with a tendency to allergies.
[7] These undesirable effects are usually mild in nature and frequently subside during, or otherwise after discontinuing the treatment.
[8] If there are signs of pseudomembranous colitis or severe hypersensitivity reactions, the treatment should be discontinued and medical treatment (see section 4.4) provided.
[9] If central nervous excitation, myoclonus or seizures occur, ampicillin should be discontinued and suitable treatment instituted.

Description of selected adverse reactions
A moderate rise in serum concentration of aspartate aminotransferase (ASAT) has been observed, particularly in infants; however, the significance of these findings is unknown. Mild, temporary rises in ASAT have been observed in people who receive larger (two to four times) and more frequent intramuscular injections than usual. Information indicates that ASAT is released at the administration site of the intramuscular injection of ampicillin sodium and that the presence of an increased amount of this enzyme in the blood is not necessarily a sign that the liver is affected.

[…]

## 4.9 Overdose

Symptoms
Typical signs of intoxication following the administration of larger amounts of ampicillin have not been observed to date. Long-term therapy is also not associated with specific toxic adverse reactions.
Toxic reactions can include nausea, vomiting, diarrhoea, electrolyte disorders, altered consciousness, coma, haemolytic reactions and acidosis.
The single administration of a larger amount of ampicillin is not acutely poisonous (toxic).The administration of very high doses can lead to oliguric renal failure and may have effects on nerve cells, for example in the form of central nervous excitation, impairments of muscular function and seizures. The risk of these undesirable effects is increased in patients with severely impaired renal function.
In individual cases, however, these effects were only observed after intravenous administration.

## 6.2 Incompatibilities

Ampicillin solutions should always be administered separately, unless compatibility with other infusion solutions or medicines has been established.
This medicinal product must not be mixed with other solutions except those mentioned in section 4.2.
Ampicillin solutions should not be mixed with aminoglycosides, metronidazole and injectable tetracycline derivatives such as oxytetracycline, rolitetracycline and doxycycline. Visual signs of incompatibility are precipitation, clouding and discoloration.