VITAMED
REKAH GROUP
Pharmaceutical Industries LTD

אפריל 2025

עדכון עלון לרופא של התכשיר:
Ceftriaxone-VIT
Powder for solution for injection

צוות רפואי נכבד,

חברת ויטאמד תעשיות פרמצבטיות בע"מ, מבקשת להודיעכם על עדכון העלון לרופא של התכשיר: **צפטריאקסון-ויט**.

בהודעה זו מצוינים רק הסעיפים בהם נעשו שינויים מהותיים בעלון לרופא, למידע מלא יש לעיין בעלון.

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות. ניתן לעיין בכתובת:

https://israeldrugs.health.gov.il/#!/medDetails/159%2042%2034699%2000

כמו כן, ניתן לקבלו מודפס ע"י פנייה לבעל הרישום:

ויטאמד תעשיות פרמצבטיות בע"מ, הטחנה 6, ת.ד. 114, בנימינה, 3055002, ישראל.

הרכב התכשיר:

Each vial of Ceftriaxone-VIT contains: Ceftriaxone Disodium Hemiheptahydrate 1.193g (corresponding to Ceftriaxone 1.000g).

התוויה מאושרת:

Ceftriaxone-VIT is indicated for the treatment of the following infections in adults and children including term neonates (from birth):
- Bacterial Meningitis
- Community acquired pneumonia
- Hospital acquired pneumonia
- Acute otitis media
- Intra-abdominal infections
- Complicated urinary tract infections (including pyelonephritis)
- Infections of bones and joints
- Complicated skin and soft tissue infections
- Gonorrhoea
- Syphilis
- Bacterial endocarditis

Ceftriaxone-VIT may be used:
- For treatment of acute exacerbations of chronic obstructive pulmonary disease in

adults.
- For treatment of disseminated Lyme borreliosis [early (stage II) and late (stage III)] in adults and children including neonates from 15 days of age.
- For pre-operative prophylaxis of surgical site infections.
- In the management of neutropenic patients with fever that is suspected to be due to a ceftriaxone susceptible bacterial infection.
- In the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Ceftriaxone-VIT should be co-administered with other antibacterial agents whenever the possible range of causative bacteria would not fall within its spectrum (see section 4.4).

Consideration should be given to official guidelines on the appropriate use of antibacterial agents.

להלן העדכונים בעלון לרופא: ההחמרות סומנו בצהוב והמחיקות סומנו בצבע אדום עם קו מחיקה.

[...]

3. PHARMACEUTICAL FORM

Powder for solution for injection.
Each vail contains almost white or yellowish crystalline powder.

4. CLINICAL PARTICULARS

[...]

4.2. Posology and method of administration

Method of administration
Intramuscular administration
Ceftriaxone-VIT can be administered by deep intramuscular injection. Intramuscular injections should be injected well within the bulk of a relatively large muscle and not more than 1 g should be injected at one site.
As the solvent used is lidocaine, the resulting solution should never be administered intravenously (see section 4.3). The information in the Summary of Product Characteristics of lidocaine should be considered.
Intravenous administration
Ceftriaxone-VIT can be administered ~~by intravenous infusion over at least 30 minutes (preferred route) or~~ by slow intravenous injection over 5 minutes. Intravenous intermittent injection should be given over 5 minutes preferably in larger veins. ~~Intravenous doses of 50 mg/kg or more in infants and children up to 12 years of age should be given by infusion.~~ In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy (see section 4.3 and 4.4). Intramuscular administration should be considered when the intravenous route is

not possible or less appropriate for the patient. For doses greater than 2 g intravenous administration should be used.
Ceftriaxone-VIT is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, ~~including continuous calcium containing infusions such as parenteral nutrition~~ because of the risk of precipitation of ceftriaxone-calcium (see section 4.3).
Diluents containing calcium, (e.g. Ringer's solution or Hartmann's solution), should not be used to reconstitute **Ceftriaxone-VIT** vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when **Ceftriaxone-VIT** is mixed with calcium-containing solutions in the same intravenous administration line. Therefore, **Ceftriaxone-VIT** and calcium-containing solutions must not be mixed or administered simultaneously (see sections 4.3, 4.4 and 6.2).
[...]

4.3 Contraindications

Hypersensitivity to ceftriaxone, to any other cephalosporin or to any of the excipients listed in section 6.1.
History of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agent (penicillins, monobactams and carbapenems).
Ceftriaxone-VIT is contraindicated in:

- Premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age)*
- Full-term neonates (up to 28 days of age):
  - with hyperbilirubinaemia, jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired*.
  - if they require (or are expected to require) intravenous calcium treatment, ~~or calcium- containing infusions~~ due to the risk of precipitation of a ceftriaxone-calcium salt (see sections 4.4, 4.8 and 6.2).

* In vitro studies have shown that ceftriaxone can displace bilirubin from its serum albumin binding sites leading to a possible risk of bilirubin encephalopathy in these patients.

Contraindications to lidocaine must be excluded before intramuscular injection of ceftriaxone when lidocaine solution is used as a solvent (see section 4.4). See information in the Summary of Product Characteristics of lidocaine, especially contraindications.
Ceftriaxone solutions containing lidocaine should never be administered intravenously.

4.4 Special warnings and precautions for use

Hypersensitivity reactions
As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported (see section 4.8). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). In case of severe hypersensitivity reactions, treatment with ceftriaxone must be discontinued immediately and adequate emergency measures must be initiated. Before beginning treatment, it should be

established whether the patient has a history of severe hypersensitivity reactions to ceftriaxone, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if ceftriaxone is given to patients with a history of non-severe hypersensitivity to other beta- lactam agents.

Severe cutaneous adverse reactions (Stevens Johnson syndrome or Lyell's syndrome/ toxic epidermal necrolysis) ~~and drug reaction with eosinophilia and systemic symptoms (DRESS) which can be life threatening or fatal~~ have been reported ~~in association of ceftriaxone treatment~~; however, the frequency of these events is not known (see section 4.8).

Interaction with calcium containing products

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full- term neonates aged less than 1 month have been described. At least one of them had received ceftriaxone and calcium at different times and through different intravenous lines. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. In vitro studies demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups.

In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium- containing intravenous solutions~~, even via different infusion lines or at different infusion sites. However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing total parenteral nutrition (TPN) solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If the use of ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion and the infusion lines flushed between solutions (see sections 4.3, 4.8, 5.2 and 6.2)~~.

[...]

Sodium

Ceftriaxone-VIT ~~1g powder for solution for injection or infusion~~ contains 83 mg sodium per ~~1g~~ vial, equivalent to 4.3% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

[...]

4.5 Interaction with other medicinal products and other forms of interaction

Calcium-containing diluents, such as Ringer's solution or Hartmann's solution, should not be used to reconstitute Ceftriaxone-VIT vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Precipitation of ceftriaxone- calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions~~, including~~

~~continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid~~. In vitro studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium (see sections 4.2, 4.3, 4.4, 4.8 and 6.2).
Concomitant use with oral anticoagulants may increase the anti-vitamin K effect and the risk of bleeding.
[...]

4.8 Undesirable effects

The most frequently reported adverse reactions for ceftriaxone are eosinophilia, leucopenia, thrombocytopenia, diarrhoea, rash, and hepatic enzymes increased.
Data to determine the frequency of ceftriaxone ADRs was derived from clinical trials.
The following convention has been used for the classification of frequency:
Very common (≥ 1/10)
Common (≥ 1/100 - < 1/10)
Uncommon (≥ 1/1,000 - < 1/100)
Rare (≥ 1/10,000 - < 1/1,000)
Not known (cannot be estimated from the available data)

System Organ Class	**Common**	**Uncommon**	**Rare**	**Not Known[a]**
Infections and infestations		Genital fungal infection	Pseudo-membranous colitis[b]	Superinfection[b]
Blood and lymphatic	Eosinophilia Leucopenia	Granulocytopenia Anaemia		Haemolytic anaemia[b]
System disorders	Thrombocytopenia	Coagulopathy		Agranulocytosis
Immune system disorders				Anaphylactic shock Anaphylactic reaction Anaphylactoid reaction Hypersensitivity[b] Jarisch-Herxheimer reaction[b]
Nervous system		Headache Dizziness	Encephalopathy	Convulsion

disorders				
Ear and labyrinth disorders				Vertigo
Cardiac disorders				Kounis syndrome
Respiratory, thoracic and mediastinal disorders			Bronchospasm	
Gastrointestinal disorders	Diarrhoea[b] Loose stools	Nausea Vomiting		Pancreatitis[b] Stomatitis Glossitis
Hepatobiliary disorders	Hepatic enzyme increased			Gall bladder precipitation[b] Kernicterus Hepatitis[c] Hepatitis cholestatic[b,c]
Skin and subcutaneous tissue disorders	Rash	Pruritus	Urticaria	Stevens Johnson Syndrome[b] Toxic epidermal necrolysis[b] Erythema multiforme Acute generalised exanthematous Pustulosis Drug reaction with eosinophilia and systemic symptoms (DRESS)[b]
Renal and urinary disorders			Haematuria Glycosuria	Oliguria Renal precipitation (reversible)
General disorders and administration site conditions		Phlebitis Injection site pain Pyrexia	Oedema Chills	
Investigations		Blood creatinine	Oedema Chills	Coombs test

		increased		false positive[b] Galactosaemia test false positive[b] Non enzymatic methods for glucose determination false positive[b]

[a] Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.

[b] See section 4.4.

[c] Usually reversible upon discontinuation of ceftriaxone.

Infections and infestations

Reports of diarrhoea following the use of ceftriaxone may be associated with *Clostridium difficile.* Appropriate fluid and electrolyte management should be instituted (see section 4.4).

Ceftriaxone-calcium salt precipitation

Rarely, severe, and in some cases, fatal, adverse reactions have been reported in pre-term and full-term neonates (aged < 28 days) who had been treated with intravenous ceftriaxone and calcium.

Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in neonates is a result of their low blood volume and the longer half-life of ceftriaxone compared with adults (see sections 4.3, 4.4, and 5.2).

Cases of ceftriaxone precipitation in the urinary tract have been reported, mostly in children treated with high doses (e.g. ≥ 80 mg/kg/day or total doses exceeding 10 grams) and who have other risk factors (e.g. dehydration, confinement to bed). This event may be asymptomatic or symptomatic and may lead to ureteric obstruction and postrenal acute renal failure, but is usually reversible upon discontinuation of ceftriaxone (see section 4.4).

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, primarily in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application - above 30 % in some studies. ~~The incidence appears to be lower with slow infusion (20 - 30 minutes).~~ This effect is usually asymptomatic, but the precipitations have been accompanied by clinical symptoms such as pain, nausea and vomiting in rare cases. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuation of ceftriaxone (see section 4.4).

[...]

בברכה,

ויטאמד תעשיות פרמצבטיות בע"מ