PHARMACODE 135

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VERACOL

Ceftriaxone 250mg, 500mg, 1g, 2g
Powder for Solution for Injection or Infusion

1. DESCRIPTION OF THE MEDICINAL PRODUCT

1.1 Name: VERACOL

1.2 Qualitative composition: Active Ingredient: Ceftriaxone Sodium Trisesquihydrate. Excipients: None

1.3 Pharmaceutical form: Powder and solvent for injectable solution

1.4 Content in active ingredient: Each vial of VERACOL contains Ceftriaxone sodium trisesquihydrate equivalent to the labelled amount of Ceftriaxone.

1.5 Description-Packaging: The product is distributed in glass vials. Each vial is packed in a carton box with an instruction leaflet and it is accompanied by a solvent ampoule.

1.6 Pharmacotherapeutic class: Antimicrobial, chemotherapeutic factor

1.7 Marketing Authorization Holder – manufacturer: DEMO S.A., Pharmaceutical Industry, 21st km National Road Athens - Lamia, 14568 Kryoneri, Athens, Greece, Tel. +30 210 8161802, Fax: +30 210 8161587.

2. WHAT YOU SHOULD KNOW ABOUT THE MEDICINE YOUR DOCTOR HAS PRESCRIBED TO YOU

2.1 General information: ***Microbiology:*** Ceftriaxone is a long acting, wide range antibiotic, which belongs to the third generation of the cephalosporins class, for parenteral use. Its antibacterial action is due to its ability to inhibit the bacterial cell wall synthesis. *In vitro* Ceftriaxone acts against a wide spectrum of both Gram-negative and Gram-positive microorganisms. Ceftriaxone has a high degree of stability in the presence of β-lactamases, penicillinases and cephalosporinases of gram-positive and gram-negative bacteria. Ceftriaxone is usually active against the following microbes *in vitro* as well as in clinical infections (see "Indications"). ***Gram-positive anaerobes:*** *Staphylococcus aureus* (susceptible to methicillin), *Staphylococci coagulase-negative, Streptococcus pyogenes* (β-haemolytic, group A), *Streptococcus agalactiae* (β-haemolytic, group B), *Streptococci* β-haemolytic (that do not belong to groups A or B), *Streptococcus viridans, Streptococcus pneumoniae.* NOTE: All staphylococcal species that are methicillin resistant are also resistant to cephalosporins, including Ceftriaxone. In general, *Enterococcus faecalis, Enterococcus faecium* and *Listeria monocytogenes* are resistant. ***Gram-negative anaerobes:*** *Acinetobacter twoffi, Acinetobacter anitratus* (mainly *A. baumanii*)*, *Aeromonas hydrophila, Alcaligenes faecalis, Alcaligenes odorans, Alcaligenes* (congener) bacteria, *Borrelia burgdorferi, Capnocytophaga spp., Citrobacter diversus* (including *C. amalonaticus*), *Citrobacter freundii*, Escherichia coli, Enterobacter cloacae*, *Enterobacter aerogenes*, Enterobacter spp.* (other)*, *Haemophilus ducreyi, Haemophilus influenzae, Haemophilus parainfluenzae, Hafnia alvei, Klebsiella oxytoca, Klebsiella pneumoniae***, *Moraxella catarrhalis* (former *Branhamella catarrhalis*), *Moraxella osloenis, Moraxella spp.* (other), *Morganella morganii, Neisseria gonorrhoeae, Neisseria meningitidis, Pasteurella multocida, Plesiomonas shigelloides, Proteus mirabilis, Proteus penneri*, Proteus vulgaris, Pseudomonas cepacia, Pseudomonas fluorescens*, Pseudomonas spp.* (other)*, *Providentia rettgeri, Providentia spp.* (other), *Salmonella typhi, Salmonella spp.* (non typhoid), *Serratia marcescens, Serratia spp.* (other), *Shigella spp., Vibrio spp., Yersinia enterocolitica, Yersinia spp.* (other). * Some isolated strains are resistant to Ceftriaxone, due to the production of chromosome encoded β-lactamase. ** Some isolated strains are resistant, due to the production of wide range β-lactamase that is transferred through plasmid. 30% of the isolated strains of *Klebsiella pneumoniae* in Greece are resistant to Ceftriaxone. NOTE: Many strains of the above-mentioned microorganisms which are multiply resistant to other antibiotics e.g. amino- and ureid-penicillines, older cephalosporins and aminoglycosides are susceptible to Ceftriaxone. *Treponema pallidum* is susceptible *in vitro* and in experimental animals. Clinical research presents a good response of the primary and secondary syphilis to treatment with Ceftriaxone. ***Anaerobic bacteria:*** *Bacteroides spp.* (gall susceptible)*, *Clostridium spp.* (except for *C. perfringens* group), *Fusobacterium nucleatum, Fusobacterium spp.* (other), *Gaffkia anaerobica* (former *Peptococcus*), *Peptostreptococcus spp.* * Some isolated strains are resistant to Ceftriaxone, due to the production of β-lactamase. NOTE: With the exception of Peptococcus and Peptostreptococcus strains, the susceptibility of the other anaerobic bacteria need to be confirmed through determination of MICs, due to the production of β-lactamase by various anaerobic bacteria strains, which inhibits Ceftriaxone. Consequently, Ceftriaxone cannot be used for empirical treatment, alternatively to clindamycin and nitroimidazoles. *Clostridium difficile* is resistant. The susceptibility to Ceftriaxone can be determined by using the diffusion method on a susceptibility disk or the dilution method in an agar or a broth, according to the standarized techniques for susceptibility testing by the National Committee for Clinical Laboratory Standardization (NCCLS), which has published the below interpretive criteria:

	Susceptible	Intermediate	Susceptible
Dilution method ***MIC (mg/L)***	≤ 8	16 - 32	≥ 64
Diffusion method (30μg Ceftriaxone disk) Inhibitory zone diameter (mm)	≥ 21	20 - 14	≤ 13

Susceptibility of various micro-organisms should be confirmed using Ceftriaxone susceptibility plates only when it has been proved *in vitro* susceptibility. In cases that the above interpretive criteria cannot be used, other standarized procedures and interpretive criteria can be used (e.g. by the DIN, ICS etc).

2.2 INDICATIONS: Infections caused by pathogens sensitive to VERACOL, e.g.: sepsis, meningitis, LYME disease: proved cases of serious assault to CNS, heart and joints, abdominal infections (peritonitis, infections of the biliary and gastrointestinal tracts), infections of the bones, joints, soft tissue, skin and of wounds, infections in patients with impaired defence mechanisms in combination with other groups of antibiotics e.g. aminoglycosides, renal and urinary tract infections, respiratory tract infections, particularly pneumonia, and ear, nose and throat infections, genital infections, including gonorrhea, Perioperative prophylaxis.

2.3 CONTRAINDICATIONS: VERACOL is contraindicated in patients with known hypersensitivity to the cephalosporin class of antibiotics. In patients hypersensitive to penicillin, the possibility of allergic cross-reactions should be borne in mind. **Neonates (≤28 days):** Veracol must not be co-administered with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition, in neonates because of the risk of precipitation of ceftriaxone-calcium salt. Cases of fatal reactions with ceftriaxone-calcium precipitates in lung and kidneys in neonates have been described. In some cases the infusion lines and the times of administration of ceftriaxone and calcium-containing solutions differed. For information regarding all other patients, see "Special Precautions and Warnings for Use" section.

2.4 SPECIAL PRECAUTIONS AND WARNINGS FOR USE: 2.4.1 As with other cephalosporins, anaphylactic shock cannot be ruled out even if a thorough patient history is taken. Anaphylactic shock requires immediate countermeasures. Pseudomembranous colitis has been reported wit nearly all antibacterial agents, including ceftriaxone.It is therefore very significant that the diagnosis in question is taken into account, in patients presenting diarrhea following the administration of the antimicrobial factors. As in the case of other antimicrobial factors re-infections by resistant microorganisms may occur. Shadows have been observed in ultrasound studies of the gallbladder. These have erroneously been interpreted as being gallstones. These appear usually after higher doses than those recommended have been administered. These shadows are deposit of calcium salts formed by ceftriaxone that is disappearing following the end or the discontinuation of ceftriaxone treatment. These findings have rarely been correlated with symptoms. In the event that these symptoms occur, a conservative non-surgical management is indicated. In such cases, whether the ceftriaxone treatment should be discontinued or not has to be decided by patient's physician.

2.4.2 Elderly: There are no special precautions for elderly patients.

2.4.3 Pregnancy: Safety throughout pregnancy has not been documented. Toxicological studies of reproduction in animals did not show any signs of embryotoxicity, teratogenesis or anyother effects with respect to fertility of the two sexes, the birth, or the peri- and post-natal development. In monkeys, no embryotoxicity or teratogenesis has been observed.

2.4.4 Lactation: It is recommended that Veracol is administered with caution to nursing mothers, taking into account the fact that ceftriaxone passes into human milk in small concentrations.

2.4.5 Children: Safety and effectiveness of ceftriaxone in newborn babies, infants and children has been documented and is described in the "Posology and Method of Administration" section. Relevant studies have shown that Ceftriaxone, like some other cephalosporines, may displace bilirubin from the serum albumin. Therefore great attention needs to be paid when administering Ceftriaxone to a newborn baby suffering from bilirubinaemia. Ceftriaxone should not be administered to any newborn, especially premature ones, which present a high risk of developing bilirybin encephalopathy. During prolonged treatment, the figured elements of the blood should be monitored regularly.

2.4.6 Effects on ability to drive and use machines: No specific precautions or warnings have been reported with respect to the effects of the medicine on the ability to drive or operate machinery.

2.4.7 Special precautions for excipients: You should not take VERACOL if you are allergic to any of its ingredients.

2.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION: No impairment of renal function has so far been observed after concurrent administration of large doses of VERACOL and potent diuretics (e.g. furosemide). There is no evidence that VERACOL increases renal toxicity of aminoglycosides. No effect similar to that of disulfiram has been demonstrated after ingestion of alcohol subsequent to the administration of VERACOL. Ceftriaxone does *not* contain an Nmethylthiotetrazole which is possibly associated with possible ethanol intolerance and bleeding problems of certain other cephalosporins. The elimination of VERACOL is not altered by probenecid. In an *in vitro* study, competitive actions were observed by combining chloramphenicol and Ceftriaxone. In patients receiving VERACOL, the Coombs test can rarely be falsely positive. VERACOL, as other antibiotics,

can give falsely positive results in galactosemia tests. Likewise, non-enzymatic methods of glucose identification in urine can give false results. Because of this, the glucose identification in urine should be performed using enzymatic methods. **INTERACTION WITH CALCIUM-CONTAINING PRODUCTS:** There are no reports to date of intravascular or pulmonary precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing IV solutions. However, the theoretical possibility exists for an interaction between ceftriaxone and IV calcium-containing solutions in patients other than neonates. Therefore, VERACOL and calcium- containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age, even via different infusion lines at different sites. As a further theoretical consideration and based on 5 half-lives of ceftriaxone, VERACOL and IV calcium-containing solutions should not be administered within 48 hours of each other in any patient (see "Contraindications" and "Posology and Administration" section). No data are available on potential interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (IV or oral).

2.6 POSOLOGY AND METHOD OF ADMINISTRATION: ***RECOMMMENDED DOSAGE:*** *Adults and children 12 years and over:* The standard therapeutic dosage is 1-2g of VERACOL once daily (every 24 hours). In severe infections, or in case of infections due to moderately susceptible microorganisms, the recommended daily doe can be increased to 4g once daily. Neonates, infants and children up to 12 years: The following dosage schemes are recommended for once daily administration: Neonates up to 28 days: a daily dose of 20-50 mg/kg body weight, not to exceed 50 mg/kg. A dose adjustment for premature neonates is not required. Hyperbilirubinemic neonates, especially prematures, should not be treated with Veracol (see "Special Precautions and Warnings for Use" section). Infants and children of up to 12 years: a daily dose of 20-80 mg/kg body weight. For children with body weights of 50kg or more, the usual adult dosage should be used. Doses of 50mg/kg or over should be given by slow intravenous infusion over at least 30 minutes. Elderly: Dosage adjustment is not required for geriatric patients. Duration of Treatment: The duration of treatment varies according to the course of the disease. As with antibiotic therapy in general, administration of Ceftriaxone should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained. Combined Treatment: An in vitro synergistic action between Ceftriaxone and aminoglycosides has been reported against many gram-negative microorganisms. Although the synergestic effect of the combination can not always estimated, it should be considered in case of severe, life-threatening infections. Due to their physical incompatibility, these two drugs should be administered separately, as recommended. Dosage Modifications: Meningitis: The recommended treatment for adults, adolescents over 12 years and children with body weights of 50 kg or more should be started with doses 50 to 100 mg/kg body weight once daily, but not exceeding 4g daily. The recommended treatment for infants and children up to 12 years should be started with doses of 50-100mg/kg body weight once daily, but not exceeding 2g daily. Neonates up to 2 weeks should not receive more than 50mg/kg body weight. As soon as the causative microorganism has been identified and its susceptibility to Ceftriaxone has been determined, the used dose can be reduced accordingly. The duration of treatment varies according to the course of the disease. *Usually a 1-2 week treatment is adequate.Gonorrhoea:* For the treatment of gonorrhoea (against both strains, those that produce penicillinase and those that do not), a singe intramuscular dose of 250 mg VERACOL is recommended. LYME Brreliosis: The dosage is 50mg/kg up to the maximum 2g in children and adults administered once daily for 14 days. Pre-operative prophylaxis: For the prevention of post-operative infections in infected or possibly infected surgical procedures, the management that is indicated in accordance with the risk of infection is a single dose of 1-2g VERACOL administered 30-90 minutes before operation. In colorectal surgery, the simultaneous (but isolated) VERACOL administration with or without 5-nitroimidazole (e.g. ornidazole), has been proved to be quite effective. Impaired renal or hepatic function: In patients with impaired renal function, there is no need to reduce the dosage of VERACOL provided liver function is intact. Only in cases of pre-terminal renal failure (creatinine clearance < 10 ml per minute) should the daily dosage be limited to 2g or less. In patients with liver damage, there is no need for the dosage to be reduced provided that the renal function is intact. In severe renal impairment accompanied by hepatic insufficiency, the plasma concentration of VERACOL should be determined at regular intervals and dosage adjusted. In patients undergoing dialysis, no additional supplementary dosing is required following the dialysis. Serum concentrations should be monitored, however, to determine whether dosage adjustments are necessary, since the elimination rate in these patients may be reduced. **METHOD OF ADMINISTRATION:** VERACOL solutions maintain their physical and chemical stability for 6 hours at room temperature (or for 24 hours at +5°C). However, generally the use of freshly prepared solutions is recommended. The colour of the solutions varies from light to dark yellow depending on their concentration and the duration of storage after reconstitution. However, colour variation does not affect the potency of the drug. ***Intramuscular injection:*** 1g VERACOL should be dissolved in 3.5 ml of 1% Lidocaine Hydrochloride injection solution, 500 mg VERACOL should be dissolved in 2 ml of of 1% Lidocaine Hydrochloride injection solution and 250 mg VERACOL should be dissolved in 2 ml of 1% Lidocaine Hydrochloride injection solution. The solution should be administered by deep intramuscular injection. Doses greater than 1g should be divided and injected at more than one site. Solutions in Lidocaine should not be administered intravenously. ***Intravenous injection:*** 1g VERACOL should be dissolved in 10 ml of Water for Injections. The injection should be administered over at least 2 - 4 minutes. ***Intravenous infusion:*** 2g VERACOL should be dissolved in 40ml of one of the following calcium-free solutions: Dextrose Injection 5% or 10%, Sodium Chloride Injection 0.9%, Sodium Chloride and Dextrose Injection (0.45% Sodium Chloride and 2.5% Dextrose), Dextran 6% in Dextrose Injection 5%, Hydroxyethyl Starch 6 - 10% infusions, Water for Injections. The infusion should be administered over at least 30 minutes. VERACOL solutions should not be mixed with solutions containing other antimicrobial drugs or with other solvents, except from the aforementioned, because there is possibility of incompatibility. Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Veracol. Particulate formation can result. Veracol and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age, even via different infusion lines at different sites (see "Contraindications" and "Interaction" sections.)

2.7 OVERDOSE: In the case of overdosage, drug concentrations would not be reduced by haemodialysis or peritoneal dialysis. There is no specific antidote. Treatment should be symptomatic.

2.8 UNDESIRABLE EFFECTS: During the use of VERACOL, the following side effects, which were reversible either spontaneously or after withdrawal of the drug, have been observed: **Gastrointestinal complaints (about 2% of cases):** loose stools or diarrhea, nausea, vomiting, stomatitis and glossitis. **Hematological changes (about 2%):** eosinophilia, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia. Isolated cases of grannulocytopenia (<500 mm3) have been reported, most of which occurred after 10 days of therapy with administration of total doses of 20g or higher. **Skin reactions (about 1%):** exanthema, allergic dermatitis, pruritus, urticaria, edema. Isolated cases of serious skin adverse effects have been reported: figured (polymorphus) erethema, Stevens-Johnson syndrome, Lyell syndrome/toxic epidermic necrolysis.

Other, rare side effects: headache and dizziness, increase in liver enzymes, gallbladder sludge, oliguria, increase in serum creatinine, mycosis of the genital tract, fever, shivering and anaphylactic or anaphylactoid reactions. Pseudomembranous enterocolitis and coagulation disorders have been reported as very rare side effects. Precipitation of the drug in renal tubules has been very rarely reported, mostly in children more than 3 years old, who had either received high daily doses (≥ 80 mg/kg/daily) or total doses exceeding 10g, and they had other risk factors (fluid reduction, restriction in bed). This fact may be symptomatic or asymptomatic; it could lead to renal failure and is reversible by discontinuing the drug. ***Local side effects:*** In rare cases, phlebitic reactions occurred after IV administration. These may be prevented by slow (two to four minutes) injection of the substance. Intramuscular injection *without* lidocaine solution is painful.

2.9 WHAT YOU SHOULD KNOW IF YOU HAVE MISSED A DOSE: If you missed a dose, please tell your doctor immediately and he will advise you about the continuation of your treatment.

2.10 EXPIRY DATE: It is indicated on the label and the outer carton. In case this date has passed, do not take this drug.

2.11 SPECIAL PRECAUTIONS FOR STORAGE: Store below 25°C.

2.12 DATE OF LAST REVISION OF THE TEXT: June 2009.

3. GENERAL INFORMATION FOR THE RATIONAL USE OF MEDICINES

- This medicine was prescribed to you by your doctor for your particular medical condition. You should not give it to other people or use it for any other condition without first consulting your doctor.
- If any problem occurs during treatment with this medicine, please consult your doctor or pharmacist immediately.
- If you have any questions about information concerning this medicine or your medical condition, do not hesitate to ask your doctor.
- In order for this medicine to be safe and effective, it should be taken according to the instructions given to you.
- To protect your health and ensure your safety, you should read carefully all the instructions provided to you.
- Do not store this medicine in bathroom closets, because heat and humidity may affect the medicine and render it harmful to your health.
- Do not keep medicines that you no longer need or that have already expired.
- Keep all medicines out of the reach and sight of children.

4. GENERAL CLASSIFICATION FOR SUPPLY

For hospital use only.

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