

May 2009

IMPORTANT CLARIFICATION OF PRESCRIBING INFORMATION

Dear Healthcare Professional:

In letters dated June 2007 and August 2007, Roche advised you of updates to the Rocephin® (ceftriaxone sodium) for Injection Prescribing Information describing the potential risk associated with concomitant use of Rocephin with calcium-containing IV solutions.

Although there were no reports to date of intravascular or pulmonary precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing IV solutions, our letters acknowledged the theoretical possibility for an interaction between ceftriaxone and IV calcium-containing solutions in patients other than neonates. Therefore, the Prescribing Information advised that Rocephin 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 the elimination pharmacokinetics of ceftriaxone, the Prescribing Information additionally stated that Rocephin and IV calcium-containing solutions should not be administered within 48 hours of each other in any patient.

At this time, we would like to inform you of a further update to the Prescribing Information in the **CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, WARNINGS, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** sections to further clarify the subject of the previous updates. This revision to the Prescribing Information considers the following:

- All relevant postmarketing safety information reported during clinical practice in patients treated with Rocephin (ie, there continue to be no reports to date of intravascular or pulmonary precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing IV solutions).
- Results from two in vitro studies that were recently conducted to assess the interaction of ceftriaxone and calcium. One study used adult plasma and the other neonatal plasma from umbilical cord blood. These studies demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium.

Accordingly, the revisions to the Prescribing Information now contraindicate the use of Rocephin in neonates (≤ 28 days of age) if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium. For all other patients, the Prescribing Information states that Rocephin must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, Rocephin and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. There is no longer the requirement to wait 48 hours between the administration of Rocephin and IV calcium-containing solutions in these patients.

Listed below are the revised paragraphs from the sections affected by this update. Please refer to the enclosed complete Prescribing Information for the full text of all information contained within these sections.

CLINICAL PHARMACOLOGY

Interaction with Calcium: Two in vitro studies, one using adult plasma and the other neonatal plasma from umbilical cord blood have been carried out to assess interaction of ceftriaxone and calcium. Ceftriaxone concentrations up to 1 mM (in excess of concentrations achieved in vivo following administration of 2 grams ceftriaxone infused over 30 minutes) were used in combination with calcium concentrations up to 12 mM (48 mg/dL). Recovery of ceftriaxone from plasma was reduced with calcium concentrations of 6 mM (24 mg/dL) or higher in adult plasma or 4 mM (16 mg/dL) or higher in neonatal plasma. This may be reflective of ceftriaxone-calcium precipitation.

CONTRAINDICATIONS

Rocephin is contraindicated in neonates if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium (see CLINICAL PHARMACOLOGY, WARNINGS and DOSAGE AND ADMINISTRATION).

A small number of cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving Rocephin and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both Rocephin and calcium-containing fluids and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom Rocephin and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates.

WARNINGS

Interaction with Calcium-Containing Products

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Rocephin vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when Rocephin is mixed with calcium-containing solutions in the same IV administration line. Rocephin must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, Rocephin 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 CLINICAL PHARMACOLOGY, CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Postmarketing Experience: In addition to the adverse reactions reported during clinical trials, the following adverse experiences have been reported during clinical practice in patients treated with Rocephin. Data are generally insufficient to allow an estimate of incidence or to establish causation.

A small number of cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving Rocephin and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both Rocephin and calcium-containing fluids and in some a precipitate was observed in the intravenous

infusion line. At least one fatality has been reported in a neonate in whom Rocephin and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates.

DOSAGE AND ADMINISTRATION

Rocephin may be administered intravenously or intramuscularly.

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Rocephin vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when Rocephin is mixed with calcium-containing solutions in the same IV administration line. Rocephin must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, Rocephin and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid (see WARNINGS).

There have been no reports of an interaction between ceftriaxone and oral calcium-containing products or interaction between intramuscular ceftriaxone and calcium-containing products (IV or oral).

NEONATES: Hyperbilirubinemic neonates, especially prematures, should not be treated with Rocephin (see **CONTRAINDICATIONS**).

Rocephin is contraindicated in neonates if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium (see **CONTRAINDICATIONS**).

COMPATIBILITY AND STABILITY:

Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Rocephin vials or to further dilute a reconstituted vial for IV administration. Particulate formation can result.

Updated Prescribing Information is enclosed for your information. In addition, healthcare professionals can access the revised Rocephin Prescribing Information at www.rocheusa.com/products/rocephin.

We encourage you to become familiar with these changes in the Prescribing Information. If you have any questions or require additional information concerning Rocephin, please contact the Roche Pharmaceuticals Service Center at 1-800-526-6367.

Roche will continue to monitor the safety of Rocephin through established reporting mechanisms and notify regulatory authorities of any serious adverse events for evaluation. We will continue to provide you with the most current Prescribing Information for Rocephin moving forward. You can assist us in monitoring the safety of Rocephin by reporting adverse events to us at 1-800-526-6367 or by FAX at 1-800-532-3931; or report serious adverse events to FDA's MedWatch reporting system by completing an online form at www.fda.gov/medwatch/report.htm, by faxing (1-800-FDA-0178), by mail using the pre-paid postage address form provided online (5600 Fishers Lane, Rockville, MD 20852-9787), or by telephone (1-800-FDA-1088).

Safety Information

Rocephin is indicated for the treatment of lower respiratory tract infections, urinary tract infections, bacterial septicemia, skin/skin structure infections, bone and joint infections, pelvic inflammatory disease, uncomplicated gonorrhea, intra-abdominal infections, acute bacterial otitis media and meningitis when caused by susceptible organisms (please see the Prescribing Information for a list of susceptible organisms). Rocephin is also indicated for surgical prophylaxis in patients undergoing certain surgical

procedures (please see the Prescribing Information for a description of these surgical procedures).

Adverse clinical effects in adults occur at levels similar to those of other cephalosporins: diarrhea (2.7%), rash (1.7%), and local reactions ($\leq 1\%$). Rocephin is contraindicated in patients with a known allergy to cephalosporins and should be used cautiously in penicillin-sensitive patients.

Hyperbilirubinemic neonates, especially prematures, should not be treated with Rocephin. Rocephin is contraindicated in neonates if they require (or are expected to require) treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition because of the risk of precipitation of ceftriaxone-calcium. Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute Rocephin vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when Rocephin is mixed with calcium-containing solutions in the same IV administration line. Rocephin must not be administered simultaneously with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site. However, in patients other than neonates, Rocephin and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.

Sincerely,

A handwritten signature in black ink, appearing to read 'Lars Birgerson', with a long horizontal flourish extending to the right.

Lars Birgerson, MD, PhD
Vice President/Head of Global Medical Affairs

Enclosure: Complete Prescribing Information for Rocephin® (ceftriaxone sodium) for Injection.