Health Canada / Santé Canada

Health Products and Food Branch
Direction générale des produits de santé et des aliments

NOTICE TO HOSPITALS
Health Canada Issued Important Safety Information on CEFTRIAXONE

October 15, 2009

To: Hospital Chief of Medical Staff

Please distribute to the relevant Departments of Surgery, Emergency Medicine, Pharmacy, Pediatrics, Anesthesia, Geriatrics, Internal Medicine, Nursing, Dentistry, Intensive Care and/or other Departments as required and other involved professional staff and **post this NOTICE** in your institution.

Subject: Updated prescribing information for all ceftriaxone products marketed in Canada

Health Canada wishes to inform you of updated prescribing information for ceftriaxone when used with calcium-containing solutions via the intravenous (IV) route. This new safety information is based on the results of 2 recent *in vitro* studies that showed an increased risk of ceftriaxone-calcium precipitates in neonatal plasma.*

The following ***key new recommendations replace*** the previous prescribing information for ceftriaxone contained in the July 31, 2008 Notice to Hospitals about international reports of neonatal deaths in association with ceftriaxone-calcium precipitates:

- **CONTRAINDICATIONS:** Ceftriaxone is contraindicated in neonates 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.

- **WARNINGS:** In patients other than neonates, ceftriaxone and calcium-containing solutions may be administered sequentially to one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.

- **WARNINGS:** Diluents containing calcium, such as Ringer's solution or Hartmann's solution, are not to be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site, because precipitation of ceftriaxone-calcium can occur.

For patients other than neonates, *these new precautions have replaced* the previous requirement for a 48-hour interval between the administration of IV ceftriaxone and IV calcium-containing solutions. Although there have been no reports of intravascular calcium-ceftriaxone precipitates in patients other than neonates treated with ceftriaxone and calcium-containing IV products, caution is warranted during IV treatment of patients outside the neonatal period.

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

Ceftriaxone is a long-acting broad spectrum cephalosporin antibiotic for parenteral use. Ceftriaxone is indicated for the treatment of lower respiratory tract infections, urinary tract infections, bacterial septicaemia, skin and skin structure infections, bone and joint infections, intra-abdominal infections, and meningitis, when caused by susceptible organisms. Ceftriaxone is also indicated for uncomplicated gonorrhoea and for prophylaxis of patients undergoing certain surgical procedures.

Ceftriaxone is marketed in Canada under various trade names. The product monograph for Rocephin® (ceftriaxone) has been updated to include this new prescribing information. The product monographs for the generic ceftriaxone products are in the process of being updated with this same safety information.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any cases of serious interaction between ceftriaxone and calcium-containing solutions or other serious or unexpected adverse reactions in patients receiving ceftriaxone should be reported to Health Canada at the following address:

Any suspected adverse reaction can be reported to:
Canada Vigilance Program
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701D
Ottawa, Ontario, K1A 0K9
Tel: 613-957-0337 or Fax: 613-957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Tel: 1-866-234-2345
Fax: 1-866-678-6789
CanadaVigilance@hc-sc.gc.ca

The AR Reporting Form and the AR Guidelines can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.

http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/ar-ei_form-eng.php
http://hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2008-ar-ei_guide-ldir/index-eng.php

For other inquiries related to this communication, please contact Health Canada at:
Lead Directorate: Bureau of Gastroenterology, Infection and Viral Diseases
E-mail: BGIVD_Enquiries@hc-sc.gc.ca
Tel: (613) 941-2566
Fax: (613) 941-1183

*Two *in vitro* studies, one using adult plasma and the other neonatal plasma from umbilical cord blood, were carried out to assess the interaction of ceftriaxone and calcium. Ceftriaxone concentrations of 0.1 – 1 mM (55 – 555 µg/ml) were incubated for 2 hours with calcium concentrations of 2 - 12 mM (80 – 480 µg/ml). Recovery of ceftriaxone from plasma was statistically significantly reduced at calcium concentrations of 6 mM (240 µg/ml) or higher in adult plasma and 4 mM (160 µg/ml) or higher in neonatal plasma. These measures included total free and protein bound ceftriaxone and calcium.