

Summary of Product Characteristics

Section 4.2 (Posology and method of administration)

Diluents containing calcium, (e.g. Ringer's solution or Hartmann's solution), should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same IV administration line. Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously (see sections 4.3, 4.4 and 6.2).

Section 4.3 (Contraindications)

Ceftriaxone is contraindicated in:

- premature newborns up to a corrected age of 41 weeks (weeks of gestation + weeks of life),
- full-term newborns (up to 28 days of age) with
 - 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) IV calcium treatment, or calcium-containing infusions because of the risk of precipitation of ceftriaxone-calcium (see sections 4.4, 4.8 and 6.2).

Section 4.4. (Special warnings and precautions for use)

Interaction with Calcium-Containing Products

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term newborns 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 newborns, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. In vitro studies demonstrated that newborns 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 IV 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 TPN solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If 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, considering the advice to flush infusion lines between solutions. (see sections 4.3, 4.8, 5.2 and 6.2).

Section 4.8 (Undesirable effects)

Rarely, severe, and in some cases fatal, adverse reactions have been reported in preterm and full-term newborns (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 newborns is due to their low blood volume and the longer half life of ceftriaxone compared with adults (see sections 4.3, 4.4 and 5.2).

Section 5.2 (Pharmacokinetic properties)

Pharmacokinetics in special clinical situations

In the first week of life, 80% of the dose is excreted in the urine; over the first month, this falls to levels similar to those in the adults. In infants aged less than 8 days the average elimination half-life is usually two to three times longer than that of young adults

Section 6.2 (Incompatibilities)

Solutions containing ceftriaxone should not be mixed with or added to other agents. In particular diluents containing calcium, (e.g. Ringer's solution, Hartmann's solution) should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Ceftriaxone must not be mixed or administered simultaneously with calcium-containing solutions (see section 4.2, 4.3, 4.4 and 4.8).

Labelling

It is proposed that the following short form of wording should be included on the vial:

Do not mix with calcium-containing solutions.

A longer form could be used on the outer packaging, i.e.

Do not mix with solutions that contain calcium, including Hartmann's, Ringers and Total Parenteral Nutrition.

Patient information leaflet

No specific wording is proposed for inclusion in the Patient Information Leaflet, as this should be suitably amended to reflect these warnings at a National level. The warning to patients should be updated to reflect that they should inform their healthcare professional if they have recently received or are about to receive calcium (rather than this being a contraindication to treatment). Where a tear-off sheet for healthcare professionals exists, this should also be amended to strengthen the warnings on incompatibilities, in line with the SmPC.