

Summary Pharmacovigilance Assessment Report on the association of ceftriaxone and calcium with precipitation when co-administered

Reason for current safety review

A recent CHMP referral procedure introduced a contraindication for ceftriaxone in newborns requiring calcium treatment (due to the risk of precipitation when these substances are co-administered). The wording agreed by CHMP has been implemented in some Member States but not others, and where warnings have been included in product information, a number of different forms of wording have been agreed. The current review aims to harmonise wording for product information in relation to this issue.

Safety concern

A number of historical cases of rarely severe adverse reactions have been reported in preterm and full-term newborns, some of them fatal. These newborns had been treated with intravenous ceftriaxone and calcium. Some of them had received ceftriaxone and calcium at different times and on different intravenous lines. Precipitations of ceftriaxone-calcium salt were observed in lung and kidneys post-mortem in some cases. However, 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.

Clinical setting

Ceftriaxone is a broad-spectrum cephalosporin antibiotic used to treat a wide range of infections (including potentially life-threatening pneumonia, septicemia and meningitis) known or likely to be due to one or more susceptible micro-organisms and when parenteral therapy is needed. Ceftriaxone can be given by deep intramuscular injection, slow intravenous injection, or by slow intravenous infusion after reconstitution of the solution, and may be used in all age groups except pre-term infants (due to the risk of bilirubin displacement).

Important aspects of the substance/product

Ceftriaxone is known to be incompatible with calcium and a specific warning to this effect is included in the 'incompatibilities' section of the SmPC. The high risk of calcium-ceftriaxone precipitation in newborns is due to their low blood volume and the longer half life of ceftriaxone compared with adults. In infants aged less than 8 days, for example, the average elimination half-life is usually two to three times longer than that of young adults. The available data suggest that the half-life of ceftriaxone in infants aged >4 weeks approaches that of adults.

Information on the data assessed

PhVWP considered spontaneously-reported cases of calcium-ceftriaxone precipitation along with published and unpublished data provided by the MAH on potential mechanisms for calcium-ceftriaxone precipitation, and possible risk factors including concentration of ceftriaxone or calcium, half-life in various age groups, plasma protein binding and glomerular filtration rate. A review of the spontaneously-reported cases suggested that almost all of the fatal cases reported with ceftriaxone and calcium treatment occurred either in premature infants or in patients <3 weeks of age. No fatal cases were reported in adults. Robust data

from studies to investigate the formation of ceftriaxone-calcium precipitates in blood or plasma were not available.

Outcome of the assessment

The risk of calcium-ceftriaxone precipitation which has been identified in neonates led CHMP to recommend a contraindication for the use of ceftriaxone in neonates requiring calcium treatment. Given the extensive clinical experience with ceftriaxone to date, the risk of calcium-ceftriaxone precipitation appears to be very small and has occurred only in very young or premature infants. Nevertheless, the lack of re-assuring data on the risk of calcium-ceftriaxone precipitation in older patients suggests a precautionary approach is appropriate in patients older than 28 days. PhVWP therefore endorsed the following for inclusion in product information:

- A contraindication in full-term newborns (up to 28 days) requiring calcium treatment
- Strengthening of existing contraindications in preterm newborns, or newborns (up to 28 days) with jaundice, or who are hypoalbuminaemic or acidotic
- Information on the risk of calcium-ceftriaxone precipitation in patients <28 days of age
- Warnings not to simultaneously infuse calcium and ceftriaxone in patients aged >28 days of age, even via different infusion lines (although these may be infused sequentially, provided different infusion lines at different sites are used, or lines are replaced or rinsed between infusions)
- In patients requiring continuous nutrition with calcium-containing TPN solutions, if no suitable alternatives are available and ceftriaxone use is essential, ceftriaxone and TPN solutions may be administered simultaneously, albeit via different infusion lines at different sites.

Specific wording for sections 4.2, 4.2, 4.4, 4.8, 5.2 and 6.2 on the SmPC was agreed by PhVWP in August 2009.

No communication at EU level on these SmPC changes is planned. Information to Health Care Professionals may be communicated at national level if considered necessary.

Annex: References

CHMP OPINION FOLLOWING AN ARTICLE 29(2)1 REFERRAL FOR Ceftriaxone Tyrol Pharma and associated names: Ceftriaxone (<http://www.emea.europa.eu/pdfs/human/referral/ceftriaxone/CeftriaxoneTyrolPharma-AnnexesI-II-II-en.pdf>)