

**MHRA**

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Dear healthcare professional,

## **Chlorhexidine solutions: risk of chemical burn injury to skin in premature infants**

We are writing to you to provide additional information regarding a recent review which was undertaken at a European level on the risk of chemical burns in neonates following the use of chlorhexidine solutions for skin antisepsis. Some information and recommendations for healthcare professionals were published in Drug Safety Update, November 2014.

(<http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON468292>).

However, we believe that those involved in the care of neonates would find it helpful to receive further information on the data that led to these recommendations, and we are writing to you as an organisation which includes such healthcare professionals in your membership. The additional information is set out below.

### **Background to the European Review**

The review was triggered by MHRA as severe adverse events had been reported in preterm newborn infants who were treated with antiseptic solutions containing chlorhexidine prior to central venous catheterisation. The review looked at data from different sources, including Yellow Card data from the UK, published literature and cumulative reviews from companies with authorised medicinal chlorhexidine solutions.

### **Cases assessed**

Overall 44 cases were identified in which neonates suffered chemical burns following the application of aqueous or alcohol based chlorhexidine solutions of different strengths. The majority of interventions were umbilical catheter insertions. Most cases occurred in extremely premature infants born at less than or equal to 26 weeks gestation or babies that weighed less than 1000g at birth; 29 cases occurred with alcohol-based chlorhexidine solutions (0.5% and 2%) and 11 cases with 2% aqueous solutions.

The severity of skin reactions ranged from erythema/severe redness to chemical burn/chemical injury, excoriation, skin breakdown. In 29 out of the 44 cases the term "burn" was used in the report and in some of these cases the burn was further characterised as large, severe, extensive, partial or full thickness. In 5 cases the chemical injury resolved but with severe sequelae, including scarring, discoloration and keloid formation. The outcome was death in 5 cases. In 4 of them the authors considered that comorbidities of prematurity primarily led to this outcome, however, a possible contributory role of the chemical injuries cannot be excluded given the severity of the injuries. In one of the fatal cases the patient was left lying on an incontinence mat soaked in this substance, causing an extensive chemical burn on the back of the neonate.

The review primarily focused on data regarding the use of chlorhexidine solutions; however, there were some literature data reporting on the use of chlorhexidine impregnated dressings in neonates and older children. Although the evidence is not extensive, these data highlighted a higher risk of cutaneous adverse events in neonates and older children with the use of chlorhexidine impregnated dressings, compared to the use of chlorhexidine solution only prior to the procedure.

Another area of concern in premature infants exposed to chlorhexidine is the potential for systemic absorption. Blood concentrations of chlorhexidine have been reported in preterm neonates following cutaneous exposure. Although it is evident that there is potential for systemic absorption of chlorhexidine following skin antisepsis in neonates, no systemic adverse reactions have been reported, including any short term neurological complications.

Data from studies examining the efficacy and safety of whole body or umbilical cord disinfection with chlorhexidine were also reviewed. Most of these studies derived from countries with high neonatal mortality rates, where different practices of disinfection (whole body or umbilical stump disinfection or intrapartum vaginal and neonatal wiping) have been tried to reduce the incidence of neonatal sepsis. Although these trials provide some reassurance for the use of chlorhexidine in term neonates, they do not provide significant safety information regarding the risks of chlorhexidine use in very and extremely preterm infants hospitalised in neonatal intensive care units (NICUs).

### **Clinical use**

Finally it was recognised that although chlorhexidine is commonly used as an antiseptic prior to catheterisation in NICUs across EU, there are no clear guidelines, either European or international, with regard to skin antisepsis prior to invasive procedures in preterm neonates. There are limited data comparing different antiseptic agents, as well as different strengths and types of cutaneous chlorhexidine solutions in neonates.

Chlorhexidine is commonly used as an antiseptic prior to catheterisation in NICUs. However, a variety of different strengths and types of chlorhexidine solutions are recommended in different hospitals without clear justification of their use. As no efficacy data were reviewed, no robust recommendations could be provided on the most efficacious products and their safe use without a negative impact on local antisepsis and increased risk of neonatal catheter-related sepsis.

### **Conclusions of the review**

From the data reviewed the following conclusions were drawn:

- Infants born at less than 32 weeks of gestational age and when chlorhexidine is applied within the first 2 weeks of life for skin disinfection prior to invasive procedures appear to be at greatest risk of skin toxicity. However, the frequency of chemical burns in neonates cannot be reliably determined as the extent of the exposure is unknown and overall reporting of adverse events in children is known to be low.
- Although the available data indicate a higher frequency of chemical burns with the use of alcoholic solutions and with higher strength solutions, there are limitations which do not allow drawing firm conclusions on which type of products are safest for use in neonates, such as:
  - a. the lack of exposure data (unknown denominator for different types of chlorhexidine products)
  - b. the lack of data from companies with certain strengths/types of chlorhexidine solutions, such as 0.5% and 2% aqueous chlorhexidine products.

It should be noted that efficacy data were not reviewed as part of this safety assessment so it was not possible to evaluate the antimicrobial profile of different chlorhexidine solutions or compare their benefit:risk profile. However, it is important to note that inadequate antiseptic regimes may lead to increased risk of neonatal sepsis and the safety concerns identified should be carefully evaluated against the risks of ineffective skin cleansing.

- The effects of burn injuries in preterm neonates, who have many associated co-morbidities of prematurity, could be very serious, including prolonged hospitalisation, infection and potentially death.
- Pooling around the umbilicus or under the infant has been identified as a significant risk factor for the occurrence of severe burns and deaths. It is necessary to change all wet or soaked materials, drapes and gowns before proceeding with catheter insertion and to avoid any prolonged contact skin exposure to chlorhexidine such as in skin folds. Dripping or pooling of the antiseptic on sheets, padding, positioning equipment, adhesive tape, and on or under the patient should be avoided.
- Some authors and hospital guidelines advise using sterile water or saline to remove/wipe off the excess chlorhexidine solution as a measure to prevent adverse skin reactions. However, others advise against this practice as it is likely to shorten the duration of the antiseptic action of chlorhexidine. Therefore, a recommendation to rinse excess chlorhexidine solution has not been made as part of this review, until further evidence becomes available.
- Many of the chlorhexidine containing products are available in multi-dose containers which are potentially associated with the use of excessive quantities in the NICU setting. Alternative dosage forms, such as single use products, should be used where such alternative options of the appropriate strength and type of chlorhexidine solution exist.

Further information on the European review can be found at:

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/PRAC\\_recommendation\\_on\\_signal/2014/09/WC500174026.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/PRAC_recommendation_on_signal/2014/09/WC500174026.pdf)

Healthcare professionals should continue to report any suspected adverse reactions to chlorhexidine or any other medicine via the Yellow Card Scheme ([www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)).

I trust you find this additional information helpful – please do not hesitate to contact me if I can be of any further assistance.

Yours sincerely,



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