



### **FDA Recommends Against Prolonged Use of Magnesium Sulfate to Stop Pre-term Labor Due to Bone Changes in Exposed Babies**

#### **Safety Announcement**

**[5-30-2013]** The U.S. Food and Drug Administration (FDA) is advising health care professionals against using magnesium sulfate injection for more than 5-7 days to stop pre-term labor in pregnant women. This use of the drug is off-label, which means that it is not an FDA-approved use of the drug. Administration of magnesium sulfate injection to pregnant women longer than 5-7 days may lead to low calcium levels and bone problems in the developing baby or fetus, including thin bones, called osteopenia, and bone breaks, called fractures. The shortest duration of treatment that can result in harm to the baby is not known (see Data Summary).

Magnesium sulfate is approved to prevent seizures in preeclampsia, a condition in which the pregnant woman develops high blood pressure and protein in the urine, and for control of seizures in eclampsia. Both preeclampsia and eclampsia are life-threatening complications that can occur during pregnancy. Preeclampsia can lead to eclampsia, seizures, stroke, multiple organ failure, and death of the woman and/or baby.

In light of this new safety information about low calcium levels and bone problems in the developing baby, the following information is being added to the drug label for Magnesium Sulfate Injection, USP 50%:

- A new *Warning* stating that continuous administration of magnesium sulfate injection beyond 5-7 days in pregnancy for the treatment of pre-term labor can cause low calcium levels and bone changes in the baby.
- A new *Teratogenic Effects* section conveying the potential harm to developing babies by changing the Pregnancy Category to D from A. This section also includes the concerns described under the new *Warning*.
  - Pregnancy Category D means there is positive evidence of human fetal risk, but the potential benefits from using the drug in pregnant women may be acceptable in certain situations despite its risks.
  - Pregnancy Category A means that adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.
- A new *Labor and Delivery* section emphasizing that continuous administration of magnesium sulfate injection to treat pre-term labor is not approved and that the safety and efficacy of use for this indication are not established.

The manufacturers of other magnesium sulfate injection products have made similar changes to their drug labels.

### **Facts about Magnesium sulfate injection, USP**

- Magnesium is an essential mineral present in the human body in large amounts, mostly in bones. People obtain most of the magnesium in their bodies through their diet.
- High or low levels of magnesium can affect the nervous system, which includes the brain, spinal cord, and nerves. The metabolism and distribution of other minerals in the body such as calcium and potassium are often linked to levels of magnesium.
- The continuous administration of magnesium sulfate injection to treat pre-term labor is not FDA-approved, which means the safety and effectiveness of this use are not established.
- Magnesium sulfate is indicated for the prevention and control of seizures in preeclampsia and eclampsia. Preeclampsia can cause a sudden, increase in blood pressure in pregnant women and can lead to eclampsia or seizures. Both preeclampsia and eclampsia are life-threatening medical conditions that require emergency care.
- One particular magnesium sulfate product is also indicated for replacement therapy in magnesium deficiency, especially with acute low blood levels of magnesium accompanied by signs of muscle spasm similar to those seen with low calcium levels.

### **Additional Information for Patients**

- Discuss any questions you have about magnesium sulfate with your health care professional.
- Pregnant women should discuss with their health care professional the possibility of going into labor before term and the risks and benefits of any treatments that may be used.
- Report any side effects to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

### **Additional Information for Health Care Professionals**

- Administration of magnesium sulfate injection beyond 5-7 days to pregnant women can cause low calcium and bone abnormalities in the fetus. The shortest duration of treatment that can result in fetal harm is not known.
- Magnesium sulfate injection should only be used during pregnancy if clearly needed. If the drug is used during pregnancy, the health care professional should inform the patient of potential harm to the fetus.
- When used in pregnant women for conditions other than its approved indication, magnesium sulfate injection should be administered only by trained obstetrical personnel in a hospital setting with appropriate obstetrical care facilities.

- Report adverse events involving magnesium sulfate to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

## **Data Summary**

FDA identified 18 case reports in FDA’s Adverse Event Reporting System (AERS) describing skeletal abnormalities in neonates exposed in utero to magnesium sulfate. All of these cases were previously described in the medical literature.<sup>1-4</sup> Magnesium sulfate was administered to the mothers for tocolysis in pregnancy. The average duration of in utero exposure to magnesium sulfate was 9.6 weeks (range 8-12 weeks), and the estimated average total maternal dose administered was 3,700 grams. The published case series describes neonates developing skeletal abnormalities related to osteopenia; some developed multiple fractures involving the ribs and long bones.<sup>4</sup> The osteopenia and fractures were transient and resolved in cases when the outcome was reported.

Based on these literature cases, it is plausible that bone abnormalities in neonates are associated with prolonged in utero exposure to magnesium sulfate. Osteopenia and fractures may result from hypermagnesemia, which in turn causes hypocalcemia in the developing fetus.<sup>1-4</sup>

FDA also reviewed published epidemiologic studies.<sup>1,5-9</sup> One study found a statistically significant increase in bone abnormalities in neonates with in utero exposure to magnesium sulfate for more than 7 days, compared to those exposed for less than 3 days.<sup>7</sup> Another study found a significant difference at birth in the serum values of magnesium, calcium, phosphorus, and osteocalcin (a marker of bone formation) between neonates unexposed to magnesium sulfate and those exposed in utero to magnesium sulfate for more than 1 week; there was no difference in radius bone mineral content in the two groups.<sup>9</sup> In these studies, the neonatal bone abnormalities described in association with in utero magnesium sulfate exposure beyond 5-7 days included radiographic findings of radiolucent transverse metaphyseal bands of long bones such as the humerus.

Most of the epidemiological studies that were reviewed were based on retrospective reviews of charts in individual hospitals; none of the reviewed studies involved large electronic health care databases.

The long-term clinical significance of altered laboratory parameters and/or radiographic findings suggestive of bone abnormalities found in these studies is unclear because long-term follow-up data are not available in many of these studies. In one study, 11 babies who had shown bone abnormalities at birth manifested no radiographic bone abnormality at 1 and 3 years of age.<sup>6</sup>

In conclusion, the case reports and epidemiological data support an association between maternal administration of magnesium sulfate for more than 5-7 days and neonatal hypocalcemia and skeletal abnormalities. It is unknown whether a shorter duration of treatment is associated with calcium and bone abnormalities in the neonate.

The epidemiological data indicate that the effects on laboratory values resolve within days of birth. However, because of short follow-up periods, the long-term bone effects could not be studied.

## References

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