19th Expert Committee on The Selection and Use of Essential Medicines

April 8-12 2013

Expert peer review on application for adding calcium carbonate (elemental calcium 500 mg)

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included - Yes
   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences) – Not applicable as no calcium supplements are listed in the EML
   c. Please provide any additional relevant information with reference
      1. Evidence supports that the calcium, given in pharmacological doses, functions as an “anti-hypertensive agent” and “vasodilator” in preventing pre-eclampsia (especially in pregnant women from areas where calcium intake is low and in those at high risk of developing eclampsia) – Reference 3 in the review

2. Assessment of safety
   a. Have all relevant studies on safety been included - Yes
   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences) - Not applicable as no calcium supplements are listed in the EML
   c. Please provide any additional relevant information with reference:
      An increase in HELLP syndrome was noted (Reference 3 in the review)

3. Assessment of cost and availability
   a. Have all relevant data on cost and availability provided - Yes
   b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences) - Not applicable as no calcium supplements are listed in the EML
   c. Please provide any additional relevant information with reference – None
   d. Is the product available in several low and middle income countries? – No

4. Assessment of public health need
   a. Please provide the public health need for this product (1-2 sentences) - Yes: For prevention of pre-eclampsia which affects less than 10% (all hypertensive disorders of pregnancy – 10%) of all pregnant women in the world in areas with low calcium intake and in women at high risk of developing eclampsia
   b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

   In areas where dietary calcium intake is low, calcium supplementation during pregnancy (At doses of 1.5–2.0 g elemental calcium/day) is recommended for the prevention of preeclampsia in all women, but especially in those at high risk of developing pre-eclampsia. 
   (Moderate-quality evidence, Strong recommendation)

   Note: Reference 8 in the application (Guideline: Calcium supplementation in pregnant women. Geneva, World Health Organization, 2012 (in press)) was not accessible
5. Are there special requirements for use or training needed for safe/effective use? - No

6. Is the proposed product registered by a stringent regulatory authority? –
No (calcium supplements are not approved for sale as medications - FDA)

7. Any other comments:

The efficacy of calcium is in pharmacological doses and it functions as a vasodilator and anti-hypertensive agent rather than in physiological doses given as a mineral supplementation

8. What is your recommendation to the committee (please provide the rationale)

Add in Section 27 with a clause “for pregnant women from areas where calcium intake is low and for those at high risk of developing eclampsia” OR add in section 12.3 with a clause for prevention of preeclampsia and high blood pressure in pregnant women especially those from areas where calcium intake is low and for those at high risk of developing eclampsia”

1. Efficacy data: The beneficial effect of reducing the risk of high blood pressure and pre-eclampsia was greatest for women with low baseline calcium intake and those selected as being at high risk. The authors agreed that the variable methods of selecting women as being at high risk limit the clinical usefulness of these pooled results (Hofmeyr GJ, Lawrie TA, Atallah ÁN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database of Systematic Reviews 2010, Issue 8. Art. No.: CD001059)

2. There was no evidence of a significant difference between women receiving calcium supplementation (>1 g/day) and women receiving a placebo with regard to the following outcomes: placental abruption, caesarean section, proteinuria, severe pre-eclampsia, eclampsia, admission of the woman to an intensive care unit, maternal death, mother’s hospital stay ≥7 days, preterm birth, low birth weight, small for gestational age newborn, admission to neonatal intensive care unit, newborn in intensive care unit ≥7 days, and stillbirth or death before discharge from hospital. Palacios C, Pena-Rosas JP. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems: RHL commentary (last revised: 1 February 2010). The WHO Reproductive Health Library; Geneva: World Health Organization.

3. Safety data: Need more information on the “increased risk” of HELLP reported in the Cochrane review

4. WHO guidelines: In areas where dietary calcium intake is low, calcium supplementation during pregnancy (At doses of 1.5–2.0 g elemental calcium/day) is recommended for the prevention of preeclampsia in all women, but especially in those at high risk of developing pre-eclampsia. (Moderate-quality evidence, Strong recommendation)


5. Applicability to low and middle income countries

a. Interferes with iron supplementation
b. Spacing the iron and calcium intake is impractical, as calcium is recommended to be taken 3 times a day, preferably with meals
c. Bioavailability of different calcium carbonate products
d. 3 tablets 3 times/ day – 9 tablets for a day, adherence may be poor
e. Exact timing to start the supplementation is not clear from the evidence
f. Dose was also not exact (Cochrane – at least 1 gm of calcium)