19\textsuperscript{th} Expert Committee on The Selection and Use of Essential Medicines

April 8-12 2013

Expert peer review on application for: Dexamethasone for lung maturation in preterm babies

Proposed formulation for inclusion: Injection: 4 mg/ml in 1-ml ampoule (as disodium phosphate salt)
For prevention of Respiratory Distress Syndrome in cases of anticipated preterm birth within 7 days, the recommended regimen is a single course of 4 doses of 6 mg dexamethasone, administered to the mother by intramuscular injections 12 hours apart.
Proposed section for inclusion: Section 29: Specific medicines for neonatal care; or section 25: Medicines acting on the respiratory tract.

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes X No (if no, please provide reference and information)

   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   Antenatal corticosteroid treatment for women at risk of preterm delivery is considered to be the most effective intervention for reducing incidence of Respiratory Distress Syndrome (RDS). Fluorinated glucocorticoid hormones cross the placenta and trigger foetal lung maturation, including the production of surfactant.

   A 2006 Cochrane review including 21 studies found that betamethasone and dexamethasone are by far the most-studied antenatal corticosteroids (ACS) and the only two with proven efficacy. Meta-analysis of 6 RCTs using dexamethasone and 12 RCTs using betamethasone showed a reduction of 31\% in neonatal mortality.

   A Cochrane meta-analysis examined the safety and efficacy of repeat courses of either betamethasone or dexamethasone and found reduced risk in incidence and severity of neonatal lung disease as well as in serious infant morbidity. There was no statistically significant difference in other primary outcomes including perinatal mortality or mean birth weight.

   c. Please provide any additional relevant information with reference

   No studies were found from low-income settings.

   Of the two main ACS drugs (dexamethasone and betamethasone), neither has been definitively shown to be superior to the other. A large trial powered to detect a difference is ongoing but results are not expected until 2015

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes X No (if no, please provide reference and information)

   For the mother: Of the six dexamethasone studies included in the 2006 Cochrane review, only one reported number of maternal deaths, of which there were none in either the treatment or control arm.

   One study showed a possibly elevated risk of sepsis and fever requiring the use of antibiotics.
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Maternal pulmonary oedema can occur when antenatal corticosteroids are used in combination with tocolytic agents. This complication is more commonly associated with maternal infection, fluid overload and multiple gestations. Pulmonary oedema has not been reported when antenatal corticosteroids are used alone.

Safety for the fetus: No increase was seen in fetal deaths (RR 0.92, 95% CI 0.56 to 1.50, 5 studies, 1420 fetuses).

The WHO Model Formulary 2008, which includes information on use of dexamethasone during pregnancy for several other indications, notes only a “risk of intrauterine growth retardation on prolonged or repeated systemic treatment.” Antenatal dexamethasone treatment should consist of a single course.

Safety for the child: No short-term adverse effects were identified in any study. Long-term data are sparse on dexamethasone, but two follow-ups found no increased risk of death in childhood. A recent observational study evaluated development of prenatally exposed children compared to control at 1 year (1554 infants), 3 years (1328 children), and 6 years (1297 children). The study found no statistically significant adverse effect of dexamethasone treatment on verbal (VIQ) or performance intelligence quotient (PIQ); or physical, mental (MDI), or psychomotor (PDI) development indices (Liu et al. 2012).

b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

Dexamethasone (same formulation proposed in the application), is already included in the current EML for three indications: section 3 Antiallergics and medicines used in anaphylaxis, subsection 8.4 Medicines used in palliative care, and subsection 17.2 Antiemetic medicines. The same formulation also appears on the complementary list under subsection 8.3 Hormones and antihormones.

c. Please provide any additional relevant information with reference

3. Assessment of cost and availability

a. Have all relevant data on safety provided

Yes X No (if no, please provide reference and information)

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)

Dexamethasone is inexpensive (< US $1 per four-injection course) and widely available, making it the lowest-cost and most accessible means of preventing RDS and deaths due to preterm birth.

Due to supply limitations and higher costs of betamethasone, dexamethasone is much more widely available in LICs and MICs.

Dexamethasone treatment is highly cost-effective at an estimated cost per case treated of US $16.25 and cost per life saved of US $634.

c. Please provide any additional relevant information with reference
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d. Is the product available in several low and middle income countries?

Dexamethasone injection is widely available at low cost throughout the developed and developing world. The International Drug Price Indicator Guide, published in collaboration with the WHO, lists suppliers including the United Nations Population Fund and Mission Pharma. The product is also available via the UNICEF catalogue.

4. Assessment of public health need
a. Please provide the public health need for this product (1-2 sentences)

In 2010, there were an estimated 15 million preterm births or 11.1% of live births worldwide. Preterm birth is a global problem, with a rate ranging from 5% in some European countries to 18% in some African countries. Over 60% of preterm births occurred in Southern Asia and sub-Saharan Africa, which contribute 52% of global live births. Preterm birth is the leading cause of neonatal deaths and the second most common cause of mortality of children under-5 years, as well as a leading contributor to the global burden of disease, due to a significant risk of disability.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable.

Yes. They are:

- Royal College of Obstetrics and Gynaecology (RCOG): Guideline, 2010

In addition Dexamethasone is included on the WHO Priority Life-Saving Medicines for Women and Children 2012 for improvement of foetal lung maturity as part of management for preterm labour.

5. Are there special requirements for use or training needed for safe/effective use?

If yes, please provide details in 1-2 sentences

Use of dexamethasone for foetal maturation requires the ability of the caregiver to roughly determine gestational age and to diagnose preterm labour. Even in high-income settings, this can be difficult to establish with certainty unless early ultrasound data are available. In the absence of such data, guidelines support that obstetricians should err on the side of overuse rather than underuse. The need for skilled evaluation means that antenatal dexamethasone treatment requires a facility setting and is currently not recommended at the community level.

ACS reduces the overall need for special facilities by reducing need for mechanical ventilation/CPAP as well as NICU admissions.

6. Is the proposed product registered by a stringent regulatory authority?

   Yes X No

   

   

Dexamethasone is widely approved for numerous indications. For use in preterm labor, dexamethasone is only known to be approved in very few countries including: Australia, and New Zealand. In nearly all other countries, its specific antenatal use is off-label.

7. Any other comments
Since each dose is 6 mg, the 1-ml packaging may involve waste of ½ ml (2 mg) per dose, or 2 ml (8 mg) per 4-dose treatment. In order to avoid this wastage, the Committee may wish to consider multi-dose vials, which are available at 4 mg/ml concentration in sizes ranging from 2 ml to 30 ml. However, it should be noted that multi-dose vials carry increased risk of contamination and infection.

8. What is your recommendation to the committee (please provide the rationale)
To include dexamethasone in the WHO EML, based on the need, the available evidence on the safety and efficacy of the medication. Since the data on efficacy and safety is similar, I agree with the application to recommend dexamethasone over betamethasone based on lower costs.