Summary of analysis of efficacy and safety of nifedipine as tocolytic in late pregnancy.

Definition
Preterm birth is the birth occurring between 20 and 36 weeks of gestation. It is a major contributor to perinatal mortality and morbidity, and affects 6-7% of births in developed countries\(^1\).

Currently there is 1 item for tocolysis on the WHO EML, Section 22. Oxytocics and antioxytocics:

22.2 Antioxytocics
- salbutamol, tablet, 4 mg (as sulfate) and injection, 50 µg (as sulfate) in 5-ml ampoule

with the footnote stating: "The public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion in the Model List will be reviewed at the next meeting of the Expert Committee."

Nifedipine is listed on the WHO EML, Section 12. Cardiovascular medicines:

12.3 Antihypertensive medicines
- nifedipine, sustained-release formulations tablet 10 mg

Nifedipine is listed on the Anatomical Therapeutic Chemical (ATC) classification index with Defined Daily Doses (DDDs) (WHO Collaborating Centre for Drug Statistics Methodology), Oslo, Norway, 2004 under section C08 Calcium channel blockers – C08C A05 Nifedipine.

The application for listing of Nifedipine, sustained-release tablets 10mg, as tocolytic is supported by strong clinical evidence of its superiority to betamimetics and magnesium sulfate in acute tocolysis – inhibiting preterm labour. The effects of nifedipine in suppression of preterm labour were critically assessed and summarised in a meta-analysis\(^2\) and a Cochrane Systematic Review\(^3\).

Meta-analysis of nifedipine versus ritodrine for suppression of preterm labour concluded that nifedipine should be the drug of choice for the suppression of pre-term labour (positive commentary of the NHS Centre for Reviews and Dissemination (CRD) of the Cochrane collaboration for the published pooled analysis)\(^4\).

Nifedipine was studied in ten out of twelve randomised controlled trials included in the Cochrane Review involving totally 1029 women. Nifedipine was compared with betamimetics (ritodrine and terbutaline (1 trial)) and magnesium sulfate (1 trial). Nicardipine was another calcium channel blocker assessed in this review.

Efficacy of tocolysis.
The advantage in efficacy of nifedipine (calcium channel blockers) vs betamimetics or magnesium sulfate was characterised by:

- reduction of the number of women giving birth within seven days of receiving treatment (relative risk (RR) 0.76 with 95% Confidence interval (CI) 0.60 to 0.97)\(^4\);
reduction of the number of women giving birth prior to 34 weeks of gestation (RR 0.83; 95% CI 0.69 to 0.99).

**Efficacy in terms of neonatal outcomes.**
Nifedipine (calcium channel blockers) demonstrated the major advantage over traditionally used tocolytics (betamimetics and magnesium sulfate) in its favourable effects on neonatal outcomes characterised by reduction of the frequency of:

- neonatal respiratory distress syndrome (RR 0.63; 95% CI 0.46 to 0.88),
- necrotising enterocolitis (RR 0.21; 95% CI 0.05 to 0.96),
- intraventricular haemorrhage (RR 0.59 95% CI 0.36 to 0.98)
- and neonatal jaundice (RR 0.73; 95% CI 0.57 to 0.93).

**Maternal side effects.**
Nifedipine (calcium channel blockers) proved much better overall safety profile compared with betamimetics and magnesium sulfate, documented by reduction in the requirement for women to have treatment ceased due to adverse drug reaction (RR 0.14; 95% CI 0.05 to 0.36),

Later clinical trial confirmed the conclusion about superiority of nifedipine in efficacy and safety in inhibiting preterm labour.

**Maintenance therapy in tocolysis.**
Benefits and harms of maintenance therapy for preventing preterm birth after threatened preterm labour with calcium channel blockers as well as with other tocolytics remain unclear and further research is warranted (Cochrane Systematic Review based on the results of 1 trial).

**Conclusion**
* High quality clinical evidence has accumulated to form a convincing argument to list nifedipine as an antioxytocic (tocolytic) for inhibiting preterm labour, tablets, 10 milligrams; on the WHO Model List of Essential Medicines.

* Modification of 9 January 2005 version requested by the reviewer after reception of the application from WHO Reproductive Health and Research on 7 February 2005.

Professor Lilia Ziganshina,
WHO Expert Committee Member, Kazan, Russian Federation
17 February 2005

---


