**NIFEDIPINE Application**

1. **Summary statement of the proposal for inclusion**

Nifedipine, a calcium channel blocker already available in WHO Model Formulary 2004, needs an indication for threatened preterm birth. **Calcium channel blockers** are effective to inhibit uterine activity (tocolytic effect). Compared with other tocolytics, calcium channel blockers used before 34 weeks of gestation reduced neonatal morbidity and were less likely to require discontinuation because of adverse effects.\(^{(1)}\)

2. **Name of the focal point in WHO submitting or supporting the application**

- **Dr Metin Gülmezoglu** UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research

3. **Name of the organization(s) consulted and/or supporting the application**

- **BMJ Knowledge** (Dr. Luis Gabriel Cuervo), BMJ Publishing Group, London, WC1H 9JR, United Kingdom.

4. **International Nonproprietary Name (INN, generic name) of the medicine**

- Nifedipine

5. **Whether listing is requested as an individual medicine or as an example of a therapeutic group**

- Calcium-channel blockers

6. **Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)**

Preterm birth affects 5-22% of pregnancies\(^{(1)}\) and is one of the main global causes of newborn deaths.\(^{(2)}\) It burdens healthcare systems, communities, and is distressful to families. Preterm babies are at higher risk of dying or suffering complications and sequels. Care of preterm babies frequently demands hospitalisation in units cared by highly skilled personnel and requiring technologically advanced equipment.

Tocolytics are used to treat women with threatened preterm birth under the premise that stopping uterine activity will reduce preterm birth and its associated complications, and will give more time for treatments aimed at maturing the baby’s lungs. Although it has been found that most tocolytics do delay delivery, not all of them have a demonstrated improvement in clinically relevant outcomes such as
morbidity, mortality or quality of life; and tocolytics frequently have important and frequent adverse effects.

Nifedipine is a frequently prescribed calcium-channel blocker listed in WHO’s Model Formulary 2004 that has a tocolytic effect. Within calcium channel blockers, nifedipine is a representative of dihydropyridine calcium channel blockers.

7. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

The biggest RCT evaluating nifedipine in women with threatened preterm labour used nifedipine in capsules.\(^{(3;4)}\) WHO’s Model Formulary 2004 has nifedipine in 10 mg sustained release tablets. A systematic review evaluating calcium-channel blockers for inhibiting preterm labour identified studies evaluating oral or sublingual administration of nifedipine capsules or nifedipine tables, but not sustained release tablets. Dosage ranges varied in studies between 30-160 mg/day. In the largest trial, nifedipine was given with a loading sublingual dose of 10 mg of a nifedipine capsule and if uterine contractions persisted, the dose was repeated every 15 minutes without exceeding 40 mg during the first hour. Maintenance was done with slow dose nifedipine at doses ranging between 60-160 mg daily. Depending on the clinical condition, the dose could be reduced progressively after 3 days.

8. Summary of comparative effectiveness in a variety of clinical settings:

- **Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)**

  A comprehensive up-to-date overview (Search date September 2003) addressing the effects of treatments to stop contractions in preterm labour was the main source of evidence.\(^{(1)}\) This review was chosen because it has been regularly updated, its search is comprehensive, has been peer reviewed for publication and follows sound reproducible methods.

  Basic data on dosage was obtained from a systematic review included in the overview and specifically looking at the effects of calcium channel blockers.\(^{(5)}\) The biggest trial included in the review was individually appraised.\(^{(4)}\)

- **Summary of available data (appraisal of quality, outcome measures, summary of results)**

  A recently published overview of the literature (Search date September 2003) assessed the clinical effects of treatments to stop contractions in preterm labour. It found that calcium channel blockers were more likely to be beneficial than other tocolytics.\(^{(1)}\) The overview found no systematic reviews or RCTs comparing calcium channel blockers with placebo, but found one Cochrane review (Search date 2002; 12 RCTs; 1029 women) comparing calcium channel blockers with other tocolytics and specifically looking at the effects of dihydropyridine class channel blockers.\(^{(5)}\) Nifedipine was the most frequently assessed Dihydropyridine (8/9 RCTs; 627/717 [87%] women) and it was always compared with ritodrine.
Dihydropyridines vs β-mimetic: compared with β-mimetics, dihydropyridines (nifedipine or nicardipine) reduced deliveries prior to 34 weeks and babies born to women allocated to dihydropyridines had higher weights.

Nifedipine vs ritodrine: women prescribed with nifedipine had less adverse drug reactions and these were less severe. Nifedipine also prolonged their pregnancies. Nifedipine also reduced neonatal respiratory distress syndrome, neonatal jaundice or admission to neonatal intensive care (see Tables).

The WHO Model Formulary 2004 doesn’t include an indication for calcium channel blockers or nifedipine to be used in preterm labour (p 242). Current evidence suggests that dyhidropyridine calcium channel blockers, and nifedipine in particular, should be a therapeutic option. The addition of a preterm labour indication for nifedipine in preterm birth is recommended. (22.1 Drugs used in obstetrics).

• Summary of available estimates of comparative effectiveness

Table 1. Selection of clinically relevant dichotomous outcomes (5)

<table>
<thead>
<tr>
<th>Dichotomous Outcomes: nifedipine versus ritodrine (5)</th>
<th>RCTs</th>
<th>AR [%]</th>
<th>AR [%]</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal adverse drug reaction (ADR)</td>
<td>5</td>
<td>44/217</td>
<td>105/209</td>
<td>0.40</td>
<td>0.30 to 0.55</td>
</tr>
<tr>
<td>Maternal ADR requiring treatment cessation</td>
<td>7</td>
<td>0/278</td>
<td>19/264</td>
<td>0.09</td>
<td>0.02 to 0.38</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>7</td>
<td>41/284</td>
<td>59/268</td>
<td>0.64</td>
<td>0.45 to 0.91</td>
</tr>
<tr>
<td>Neonatal jaundice</td>
<td>2</td>
<td>51/118</td>
<td>66/109</td>
<td>0.73</td>
<td>0.57 to 0.93</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>7</td>
<td>11/269</td>
<td>7/260</td>
<td>1.39</td>
<td>0.60 to 3.24 [NS]</td>
</tr>
<tr>
<td>Perinatal mortality without congenital malf.</td>
<td>7</td>
<td>9/269</td>
<td>7/260</td>
<td>1.20</td>
<td>0.49 to 2.94 [NS]</td>
</tr>
<tr>
<td>Fetal death</td>
<td>7</td>
<td>1/269</td>
<td>0/260</td>
<td>3.00</td>
<td>0.13 to 71.1 [NS]</td>
</tr>
<tr>
<td>Intraventricular haemorrhage</td>
<td>2</td>
<td>19/128</td>
<td>29/123</td>
<td>0.62</td>
<td>0.37 to 1.04 [NS]</td>
</tr>
<tr>
<td>Neonatal enterocolitis</td>
<td>2</td>
<td>1/121</td>
<td>6/113</td>
<td>0.21</td>
<td>0.04 to 1.25 [NS]</td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>3</td>
<td>24/148</td>
<td>31/141</td>
<td>0.75</td>
<td>0.47 to 1.19 [NS]</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>1</td>
<td>0/95</td>
<td>4/90</td>
<td>0.11</td>
<td>0.01 to 1.93 [NS]</td>
</tr>
</tbody>
</table>

Table 2. Selection of clinically relevant continuous outcomes (5)

<table>
<thead>
<tr>
<th>Continuous outcomes: nifedipine versus ritodrine</th>
<th>RCTs</th>
<th>Women</th>
<th>WMD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy prolongation (days)</td>
<td>5</td>
<td>381</td>
<td>8.2 days</td>
<td>3.7 days to 12.8 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Continuous outcomes: Dihydropyridine (nifedipine/nicardipine) versus β-mimetic (ritodrine/salbutamol)</th>
<th>RCTs</th>
<th>Women</th>
<th>WMD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (grams)</td>
<td>5</td>
<td>426</td>
<td>122.7 grams</td>
<td>3.5 g to 242 g</td>
</tr>
<tr>
<td>Gestational age at birth</td>
<td>4</td>
<td>376</td>
<td>0.83 weeks</td>
<td>0.21 w to 1.44 w</td>
</tr>
</tbody>
</table>
9. **Summary of comparative evidence on safety:**

- **Estimate of total patient exposure to date**

  Nifedipine has been widely used for years throughout the world and is probably the most widely used calcium channel blocker. It was estimated in 1998 that in England nifedipine had around 5 million prescriptions.\(^6\) In 2003 the Department of Health for England reported over 4 million prescriptions of nifedipine (30 different preparations). Statistics published by the General Practice Research Database (GPRD) show that over 16,000 prescriptions of nifedipine were given to pregnant women in 2002.\(^7\)

- **Description of adverse effects/reactions**

  Pharmacokinetic studies and observational studies provide most of the existing information on harms. There is a paucity of comparative clinical harms information (e.g. from RCTs) allowing good estimates on frequency/magnitude of adverse events.

  The overview found no RCTs comparing tocolytic treatment with calcium channel blockers versus placebo.\(^1\) The Cochrane review identified by the overview found that compared with ritodrine, nifedipine reduced overall maternal adverse drug reactions as well as adverse drug reactions leading to discontinuation of treatment (see above).\(^5\) The Cochrane review didn’t report on specific adverse events.\(^1\)

Some of the best known adverse effects are associated with vasodilatory action and often diminish on continued therapy. These include dizziness, flushing, headache, hypotension, peripheral oedema, tachycardia and palpitations. Also nausea and other gastrointestinal disturbances, increased micturition frequency, lethargy, eye pain and mental depression. People may also have complications attributed to an abrupt decrease in blood pressure such as cerebral or myocardial ischaemia or transient blindness. Reports have been made for rashes, fever, liver function abnormalities, gingival hyperplasia and hypersensitivity reactions.

Overdosage may lead to bradycardia and hypotension, and nifedipine is reported to be teratogenic in animals. Oral acute overdosage should be treated by emptying the stomach and administering gastric lavage plus supportive and symptomatic care.

Interactions: grapefruit juice greatly increases the bioavailability of oral nifedipine, hence it shouldn’t be taken concomitantly. Drugs that increase its bioavailability include histamine H2-receptor antagonists (e.g. cimetidine), azoles (e.g. itraconazole) and sodium valproate. Alcohol can also inhibit its metabolism, increasing its effect. When given concurrently with other calcium channel blockers, its plasma concentrations can be significantly increased. Nifedipine may alter insuline and glucose response, therefore diabetic patients may need to adjust insulin dose.

The effects of nifedipine may be lessened by quinine, carbamazepine, phenobarbitone, phenytoin and rifampicin.

The combination of nifedipine and magnesium salts in 2 women with pre-eclampsia lead to profound hypotension. There is a report of a woman who developed
neuromuscular blockade after receiving magnesium and nifedipine. Combination with betablockers can result too in severe hypotension.

Nifedipine may facilitate cardiac arrest during induction of anaesthesia by sensitizing the carotid sinus. It reduces clearance of lithium

- **Identification of variation in safety due to health systems and patient factors**

- **Summary of comparative safety against comparators**

**Table 2. Selection of comparative data on harms**

<table>
<thead>
<tr>
<th>Dichotomous Outcomes: nifedipine versus ritodrine (5)</th>
<th>RCTs</th>
<th>AR [%] Nifedipine</th>
<th>AR [%] Ritodrine</th>
<th>RR</th>
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<tr>
<td>Maternal adverse drug reaction (ADR)</td>
<td>5</td>
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</tr>
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</table>

**10. Summary of available data on comparative cost1 and cost-effectiveness within the pharmacological class or therapeutic group:**

- **Range of costs of the proposed medicine**

In the UK, the cost of 10 mg (modified release) tablet is about £0.08-£0.17.[BNF 47] The Department of Health of England show in their statistics 30 different preparations for nifedipine, of which 8 are generic. The table below provides a summary of the costs and prescription of generic preparations for England in 2003.(8)

<table>
<thead>
<tr>
<th>Units</th>
<th>Prescriptions (thousands)</th>
<th>Units prescribed (thousands)</th>
<th>Average cost per prescription (£)</th>
<th>Average unit cost (£)</th>
<th>Units per prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caps 10mg</td>
<td>82.9</td>
<td>7,596.4</td>
<td>4.67</td>
<td>0.05</td>
<td>91.62</td>
</tr>
<tr>
<td>Caps 5mg</td>
<td>78.6</td>
<td>6,494.0</td>
<td>3.24</td>
<td>0.04</td>
<td>82.60</td>
</tr>
<tr>
<td>Drops 2%</td>
<td>0.1</td>
<td>2.2</td>
<td>61.66</td>
<td>1.54</td>
<td>40.05</td>
</tr>
<tr>
<td>Liquid Spec 100mg/5ml</td>
<td>0.1</td>
<td>1.8</td>
<td>50.92</td>
<td>1.46</td>
<td>34.96</td>
</tr>
<tr>
<td>Tab 10mg M/R</td>
<td>3.1</td>
<td>236.2</td>
<td>7.14</td>
<td>0.09</td>
<td>75.61</td>
</tr>
<tr>
<td>Tab 20mg M/R</td>
<td>11.2</td>
<td>846.1</td>
<td>10.90</td>
<td>0.14</td>
<td>75.50</td>
</tr>
<tr>
<td>Tab 30mg M/R</td>
<td>0.7</td>
<td>32.3</td>
<td>16.92</td>
<td>0.35</td>
<td>47.69</td>
</tr>
<tr>
<td>Tab 60mg M/R</td>
<td>111.7</td>
<td>4,705.3</td>
<td>23.18</td>
<td>0.55</td>
<td>42.14</td>
</tr>
</tbody>
</table>

*M/R stands for "Modified release"

- **Comparative cost-effectiveness presented as range of cost per routine outcome** (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)
11. **Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)**

12. **Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)**

BP 1998: Nifedipine capsules ; USP23: Nifedipine capsules ; Chinese; European; Japanese

13. **Proposed (new/adapted) text for the WHO Model Formulary**

1. Index “preterm birth”; “premature birth”; “premature labour”; “premature labour”; “preterm delivery”; “premature delivery”; “labour, premature”; “labour, premature”; “nifedipine/premature labour”.
2. Add Nifedipine under section “22.1 Drugs used in obstetrics”

**Nifedipine**

Nifedipine is a representative dihydropyridin calcium-channel blocker, and has a tocolytic effect.

*Sustained release*, (modified-release) tablets, nifedipine 10 mg.

**uses:** Threatened preterm labour: compared with betamimetics (e.g. salbutamol) nifedipine prolongs pregnancy (average 8 additional days), reduces the risk of respiratory distress syndrome (pulmonary maturation with corticosteroids should still be used), and reduces neonatal jaundice and the incidence and severity of maternal adverse drug reactions. Nifedipine may also be used late in pregnancy for pregnancy induced hypertension.

**Contraindications:** cardiogenic shock; advanced aortic stenosis; within 1 month of myocardial infarction; unstable or acute attacks of angina; porphyria; hypotension.

**Precautions:** The safety and effectiveness of nifedipine in intrapartum fetal distress and placenta previa has not been properly evaluated. Discontinue if ischemic pain is experienced following its administration. Use with caution in women with poor cardiac reserve; heart failure or significantly impaired left ventricular function; reduce dose in hepatic impairment (Appendix 5); diabetes mellitus; prolonged labour; breastfeeding (Appendix 3); avoid grapefruit juice (may affect metabolism). Store in airtight container and protect from light. **Interactions:** Appendix 1.

**Dosage:** In threatened preterm labour, give an oral loading dose of 10-40 mg in the first hour and a maintenance daily dose of 60-160 mg (e.g. 30 mg twice daily by mouth) until week 34 of gestation. Sustained release nifedipine can be given twice daily with or after food. Depending on clinical condition, the dose can be progressively reduced after 3 days.

**Adverse effects:** maternal adverse effects requiring treatment cessation are uncommon with nifedipine, and nifedipine has a lower
incidence of maternal adverse drug reactions, compared with betamimetics. Adverse effects associated with nifedipine include dizziness, headache, flushing, hypotension, lethargy; tachycardia, palpitations; short-acting preparations may induce an exaggerated fall in blood pressure and reflex tachycardia which may lead to myocardial or cerebrovascular ischaemia; gravitational oedema, rash (erythema multiforme reported), pruritus, urticaria, nausea, constipation or diarrhoea, increased frequency of micturition, eye pain, visual disturbances, gum hyperplasia, asthenia, paraesthesia, myalgia, tremor, impotence, gynaecomastia; depression, telangiectasia, cholestasis, jaundice reported. Women receiving insulin will need careful monitoring and dose adjustment because nifedipine alters glucose metabolism. In overdosage, stomach should be emptied by lavage.

1 Information on cost and cost-effectiveness should preferably refer to average generic world market prices as listed in the International Drug Price Indicator Guide, an essential medicines pricing service provided by WHO and maintained by Management Sciences for Health. If this information is not available, other international sources, such as the WHO, UNICEF and Médecins sans Frontières price information service, can be used. All cost analyses should specify the source of the price information.

Reference List


Conflicts of interest: none declared by LGC. Financial and logistical support to conduct this application have been provided by WHO and BMJ Knowledge

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