Critical limb ischaemia in peripheral vascular disease: intravenous iloprost

Evidence summary
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Key points from the evidence

The content of this evidence summary was up-to-date in December 2013. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

A Cochrane review of low quality studies of prostanoids in people with critical limb ischaemia unsuitable for surgery found that compared with placebo, intravenous iloprost statistically significantly reduced major amputations, improved rest-pain relief, and improved ulcer healing. The benefit of intravenous iloprost on total amputations (major plus minor) was not statistically significant. In a randomised controlled trial (RCT) in people undergoing femorodistal bypass surgery for critical limb ischaemia, perioperative intravenous and intra-graft iloprost did not improve graft patency or clinical status, or reduce amputations at 1-year follow-up compared with placebo. Adverse events were more common with intravenous iloprost than with placebo and included pain at the infusion site, headache, flushing, nausea and vomiting, and hypotension.

Regulatory status: Iloprost as an infusion solution is not licensed in the UK.

The topic was prioritised because there was a high volume of requests from the NHS for information on this topic and potential for variation in practice.
Effectiveness

- In a Cochrane review of prostanoids for people with critical limb ischaemia unsuitable for surgery, intravenous iloprost statistically significantly reduced major amputations, improved rest-pain relief and improved ulcer healing compared with placebo. The effect on total amputations (major plus minor) was not statistically significant. The quality of the evidence was graded as low or very low using the GRADE approach.

- In an RCT in people undergoing femorodistal bypass surgery for critical limb ischaemia; perioperative intravenous and intra-graft iloprost compared with placebo did not improve graft patency, clinical status, or reduce amputations at 1 year follow up.

Safety

- Common adverse events associated with intravenous iloprost in the Cochrane review and RCT included pain at the infusion site, headache, flushing, nausea and vomiting, and hypotension.

- A dose-comparison RCT included in the Cochrane review found a significant dose response in adverse events with intravenous iloprost.

- The RCT in people undergoing femorodistal bypass surgery for critical limb ischaemia reported there was no difference between the placebo and iloprost groups in major adverse events such as myocardial infarction, cerebrovascular accident or death from any cause in the fortnight after surgery.

Patient factors

- Administered intravenously in secondary care.

Resource implications

- Iloprost is unlicensed in the UK and can be supplied on request from the manufacturer. No costs could be obtained from standard published sources or the manufacturer.¹

¹ informal sources suggest that the cost is around £100 for a single 50 microgram ampoule, equating to around £3000 for a 4 week course.
**Key points**

Iloprost as an infusion solution is not licensed in the UK. It can be supplied on request from the manufacturer, for use by prescribers for individual patients at their sole responsibility. This summary is based on evidence from a Cochrane review of prostanoids for critical limb ischaemia ([Ruffolo et al. 2010](#)) and an RCT of perioperative intravenous iloprost in people with critical limb ischaemia undergoing femorodistal bypass grafting surgery ([Iloprost Bypass International Study Group [IBISG] 1996](#)).

The Cochrane review included 5 placebo-controlled RCTs of intravenous iloprost in people with critical limb ischaemia unsuitable for rescue or reconstructive intervention (n=604). Meta-analyses of the included RCTs were performed for the outcomes rest pain relief, ulcer healing, total amputations, major amputations and adverse events. Each meta-analysis included 3 of the RCTs, and each RCT contributed to at least 1 meta-analysis. The review found that daily intravenous iloprost infusions given for between 2 and 4 weeks, compared with placebo, statistically significantly:

- reduced major amputations at a mean follow-up of 21.3 weeks (n=318, 30.6% with intravenous iloprost compared with 44.3% with placebo risk ratio [RR] 0.69, 95% confidence interval [CI] 0.52 to 0.93)
- improved rest-pain relief at a mean follow-up of 14 weeks (n=318, 56.4% with intravenous iloprost compared with 36.6% with placebo, RR 1.54, 95% CI 1.19 to 1.99)
- improved ulcer healing at a mean follow-up of 14.7 weeks (n=367, 50.9% with intravenous iloprost compared with 28.3% with placebo, RR 1.80, 95% CI 1.29 to 2.50).

Intravenous iloprost infusions did not statistically significantly reduce total amputations (major plus minor) compared with placebo at a mean follow-up of 21.3 weeks (n=318, 36.6% compared with 46.3% respectively, RR 0.79, 95% CI 0.60 to 1.03).

One large RCT ([Iloprost Bypass International Study Group [IBISG] 1996](#); n=528) assessed intravenous iloprost given for 3 days perioperatively plus an intra-operative intra-graft dose in people having femorodistal bypass surgery for critical limb ischaemia. It found that iloprost did not improve graft patency or clinical status, or reduce amputations at 1-year follow-up compared with placebo.

Both the Cochrane review and perioperative RCT found that intravenous iloprost was associated with an increased risk of adverse events compared with placebo (absolute rates in the Cochrane...
review meta-analysis were 83.2% with iloprost compared with 40.6% with placebo; RR 2.05, 95% CI 1.68 to 2.49). Common adverse events with intravenous iloprost included pain at the infusion site, headache, flushing, nausea and vomiting, and hypotension. There was no difference between the iloprost and placebo groups in major adverse events such as myocardial infarction, cerebrovascular accident or death from any cause in the fortnight after surgery in the perioperative RCT of people having bypass surgery.

The Cochrane review also included 1 RCT (n=302) comparing different doses of intravenous iloprost. This RCT found a statistically significant dose response in adverse events with intravenous iloprost, but not in efficacy.

The RCTs in the Cochrane review and the perioperative RCT included varying populations and were mostly carried out in the 1990s, so it is not clear to what extent they would be representative of current clinical practice, including current definitions of critical limb ischaemia. In addition, the trials were of poor methodological quality. The evidence supporting the meta-analysed outcomes in the Cochrane review was graded as low or very low quality using the GRADE approach. The trials did not provide evidence about the longer-term efficacy of intravenous iloprost.

Because intravenous iloprost is unlicensed in the UK, no costs could be obtained from standard published sources or the manufacturer. No data were identified that reported the extent to which intravenous iloprost is currently being used to treat critical limb ischaemia in the UK.

About this evidence summary

‘Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, but this summary is not NICE guidance.
Overview for healthcare professionals

Regulatory status of iloprost

In the UK, the nebulised form of iloprost (Ventavis 10 microgram/ml, Bayer) is licensed for treating adults with primary pulmonary hypertension, classified as New York Heart Association (NYHA) functional class III, to improve exercise capacity and symptoms.

The intravenous infusion form of iloprost (brand names include Ilomedin, Ilomedine, or Endopro) is not licensed in the UK for any indication. It is supplied by the manufacturer in the UK, on request, for use by prescribers for individual patients at their sole responsibility.

Ilomedin is licensed in some other countries and includes the following indications (English translation of Dutch summary of product characteristics [SPC] for Ilomedin concentrate for infusion solution 0.1 mg/ml; note this SPC is not an approved UK regulatory document):

- Treatment of severe, chronic ischaemia in the extremities (peripheral arterial occlusive disease [PAOD], Fontaine stages III and IV), in cases where reconstructive vascular surgery or percutaneous transluminal angioplasty is no longer possible. This population would include those with critical limb ischemia as a result of PAOD.
- Advanced thromboangiitis obliterans (Buerger's disease) with severe ischaemia in the extremities, in cases where revascularisation is not indicated.

The approved indications vary between countries.

In the UK, use of the iloprost intravenous infusion solution for any indication would be unlicensed.

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using iloprost outside its authorised indication.

Evidence statements

- One Cochrane review included 5 placebo-controlled randomised controlled trials (RCTs) of intravenous iloprost in people with critical limb ischaemia unsuitable for rescue or reconstructive intervention (Ruffolo et al. 2010). It pooled data from these RCTs, with each meta-analysis including data from 3 out of the 5 RCTs (318 to 378 people). Each of the 5 RCTs contributed to at least 1 meta-analysis.
Meta-analyses performed as part of the review found that, compared with placebo, daily intravenous iloprost infusions given for between 2 and 4 weeks statistically significantly reduced major amputations (risk ratio [RR] 0.69, 95% confidence interval [CI] 0.52 to 0.93) but not total amputations (RR 0.79, 95% CI 0.60 to 1.03) at 21.3 weeks' follow-up. Intravenous iloprost also statistically significantly improved rest-pain relief (RR 1.54, 95% CI 1.19 to 1.99) and ulcer healing (RR 1.80, 95% CI 1.29 to 2.50) compared with placebo at 14 to 14.7 weeks' follow-up.

The individual studies were all rated as being at moderate risk of bias. The review graded the quality of the body of evidence for the meta-analysed outcomes to be of low to very low quality (the latter for ulcer healing only) using the GRADE approach. The review concluded that there was no conclusive evidence of long-term effectiveness and safety of prostanoids such as intravenous iloprost for treating critical limb ischaemia.

One multicentre double-blind RCT (n=528) in people receiving femorodistal bypass surgery for critical limb ischaemia found that iloprost given as an intravenous infusion perioperatively over 3 days plus an intra-operative intra-graft dose did not improve bypass graft patency, improve clinical status, or reduce amputations over 12 months compared with placebo (Iloprost Bypass International Study Group [IBISG] 1996).

The perioperative RCT used a relatively short treatment period of 3 days, and there were some imbalances between the groups which may have favoured the placebo group.

These RCTs included varying populations and were carried out in the 1990s, so it is not clear to what extent they would be representative of current clinical practice.

Both the Cochrane review and the perioperative RCT found that iloprost was associated with an increased risk of adverse events compared with placebo (systematic review meta-analysis RR 2.05, 95% CI 1.68 to 2.49). Common adverse events with intravenous iloprost included pain at the infusion site, headache, flushing, nausea and vomiting, and hypotension.

In the perioperative RCT, the 3-day course of perioperative iloprost did not increase major adverse events such as myocardial infarction, cerebrovascular accident or death from any cause compared with placebo in the fortnight after the operation.

Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the section.

This evidence summary includes:
One Cochrane review of RCTs assessing the use of prostanoids in people with critical limb ischaemia unsuitable for rescue or reconstructive intervention (Ruffolo et al. 2010). The review contained 20 RCTs of prostanoids including 7 that assessed intravenous iloprost: 5 placebo-controlled RCTs, 1 dose-response RCT, and 1 crossover RCT comparing intravenous iloprost with another prostanoid (prostaglandin E1; PGE1).

One RCT of perioperative intravenous iloprost and intra-operative intra-graft iloprost in people having femorodistal bypass surgery for critical limb ischaemia (IBISG 1996).

**Efficacy**

The Cochrane review found that intravenous iloprost given daily for 2 to 4 weeks in people with critical limb ischaemia unsuitable for rescue or reconstructive intervention statistically significantly reduced major amputations at a mean follow-up of 21.3 weeks compared with placebo (n=318, risk ratio [RR] 0.69, 95% CI 0.52 to 0.93). Total amputations (major plus minor) at a mean follow-up of 21.3 weeks were not statistically significantly reduced compared with placebo (n=318, RR 0.79, 95% CI 0.60 to 1.03).

Relief from rest pain and ulcer healing was statistically significantly improved by intravenous iloprost compared with placebo (relief from rest pain: mean follow-up 14 weeks, n=318, RR 1.54, 95% CI 1.19 to 1.99; and, ulcer healing: mean follow-up 14.7 weeks, n=367, RR 1.80, 95% CI 1.29 to 2.50).

The dose-response RCT included in the review found no evidence of a dose response in efficacy outcomes for intravenous iloprost. The small crossover RCT comparing short infusions of intravenous iloprost and PGE1 did not report on clinical outcomes.

The perioperative RCT in people having femorodistal bypass surgery for critical limb ischaemia found that intravenous iloprost given for 3 days perioperatively plus an intra-operative intra-graft dose of iloprost did not improve graft patency or clinical status, or reduce amputations at 1-year follow-up compared with placebo.

**Table 1 Summary of Cochrane review of intravenous iloprost in people with critical limb ischaemia not suitable for surgery**

(Ruffolo et al. 2010)
Randomised n=328 n=276 5 placebo-controlled RCTs included; 3 RCTs included in the meta-analyses. Each of the 5 RCTs contributed to at least 1 meta-analysis

**Efficacy**

n varied by outcome, see individual outcomes for n analysed

**Primary outcomes of review**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control</th>
<th>Intervention</th>
<th>RR</th>
<th>95% CI</th>
<th>Heterogeneity</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total amputations (n=318); mean follow-up 21.3 weeks</td>
<td>36.6%</td>
<td>46.3%</td>
<td>0.79</td>
<td>0.60 to 1.03</td>
<td>I²=0%, p=0.46</td>
<td>low</td>
</tr>
<tr>
<td>Major amputations (n=318); mean follow-up 21.3 weeks</td>
<td>30.6%</td>
<td>44.3%</td>
<td>0.69</td>
<td>0.52 to 0.93</td>
<td>I²=0%, p=0.93</td>
<td>low</td>
</tr>
</tbody>
</table>

**Selected secondary outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control</th>
<th>Intervention</th>
<th>RR</th>
<th>95% CI</th>
<th>Heterogeneity</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest-pain relief (n=318); mean follow-up 14 weeks</td>
<td>56.4%</td>
<td>36.6%</td>
<td>1.54</td>
<td>1.19 to 1.99</td>
<td>I²=12%, p=0.32</td>
<td>low</td>
</tr>
<tr>
<td>Ulcer healing (n=367); mean follow-up 14.7 weeks</td>
<td>50.9%</td>
<td>28.3%</td>
<td>1.80</td>
<td>1.29 to 2.50</td>
<td>I²=30%, p=0.24</td>
<td>very low</td>
</tr>
</tbody>
</table>

**Safety**

See individual outcomes for n analysed

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control</th>
<th>Intervention</th>
<th>RR</th>
<th>95% CI</th>
<th>Heterogeneity</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events (n=378); mean follow-up 21.3 weeks</td>
<td>83.2%</td>
<td>40.6%</td>
<td>2.05</td>
<td>1.68 to 2.49</td>
<td>I²=0%, p=0.98</td>
<td>low</td>
</tr>
</tbody>
</table>
Abbreviations: CI, confidence interval; \(I^2\), percentage of total variation across studies that is due to heterogeneity rather than chance; n, number of patients; p, p value; RCT, randomised controlled trial; RR, risk ratio.

\(^a\) Absolute risks quoted are taken from the Cochrane review's summary of findings table for the intravenous iloprost versus placebo comparison. These figures are different to the raw absolute risks for the iloprost group as they take into account study weighting in the meta-analysis (that is, they are calculated by multiplying the absolute risk in the placebo group by the RR from the meta-analysis).

\(^b\) Quality of evidence as reported in the Cochrane review's summary of findings table, using GRADE approach.

Table 2 Summary of RCT of intravenous iloprost used perioperatively in people having femorodistal bypass surgery for critical limb ischaemia

(IBISG 1996)

<table>
<thead>
<tr>
<th></th>
<th>Perioperative intravenous iloprost (plus intra-graft bolus iloprost)</th>
<th>Placebo</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised</td>
<td>n=NR</td>
<td>n=NR</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>n=267</td>
<td>n=250</td>
<td></td>
</tr>
<tr>
<td>Primary outcomes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary patency over 12 months (vein grafts)</td>
<td>Displayed graphically, figures NR</td>
<td>Displayed graphically, figures NR</td>
<td>p=0.81</td>
</tr>
<tr>
<td>Primary patency over 12 months (prosthetic grafts)</td>
<td>Displayed graphically, figures NR</td>
<td>Displayed graphically, figures NR</td>
<td>p=0.49</td>
</tr>
<tr>
<td>Selected secondary outcomes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary graft patency over 12 months (vein grafts)</td>
<td>NR</td>
<td>NR</td>
<td>p=0.42</td>
</tr>
</tbody>
</table>
### Safety

Meta-analysis of RCTs of intravenous iloprost in people with critical limb ischaemia unsuitable for surgery included in the Cochrane review found that about twice as many people experienced adverse events with intravenous iloprost compared with placebo. The review also included an RCT that compared varying doses of iloprost and found a statistically significant dose response in adverse events with intravenous iloprost (p<0.001). The RCT of perioperative intravenous iloprost

<table>
<thead>
<tr>
<th></th>
<th>Prosthetic Grafts</th>
<th>Vein Grafts</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary graft patency</td>
<td>NR</td>
<td>NR</td>
<td>p=0.77</td>
</tr>
<tr>
<td>over 12 months (prosthetic grafts)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limb salvage rates at 12 months (vein grafts)</td>
<td>81.8%</td>
<td>80.5%</td>
<td>Reported as not significant; p value NR</td>
</tr>
<tr>
<td>Limb salvage rates at 12 months (prosthetic grafts)</td>
<td>73.7%</td>
<td>71.4%</td>
<td>Reported as not significant; p value NR</td>
</tr>
<tr>
<td>Clinical status (Fontaine stage, amputation, or death)</td>
<td>NR by group</td>
<td>NR by group</td>
<td>Reported as not significant; p value NR</td>
</tr>
<tr>
<td>Safety</td>
<td>n=267</td>
<td>n=250</td>
<td></td>
</tr>
<tr>
<td>Intra-operative hypotension</td>
<td>14.6% (39/267)</td>
<td>4.0% (10/250)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Post-operative adverse events</td>
<td>57.7% (154/267)</td>
<td>37.2% (93/250)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction in 14 days after surgery</td>
<td>3.7% (10/267)</td>
<td>4.4% (11/250)</td>
<td>Difference reported as not significant, p value not reported</td>
</tr>
<tr>
<td>Cerebrovascular accident in 14 days after surgery</td>
<td>1.1% (3/267)</td>
<td>0.8% (2/250)</td>
<td>Difference reported as not significant, p value not reported</td>
</tr>
<tr>
<td>Death from any cause in 14 days after surgery</td>
<td>3.4% (9/267)</td>
<td>2.4% (6/250)</td>
<td>Difference reported as not significant, p value not reported</td>
</tr>
</tbody>
</table>

**Abbreviations:** n, number of patients; NR, not reported; RR, relative risk.
and intra-operative intra-graft iloprost found that, compared with placebo, iloprost increased intraoperative adverse events and post-operative adverse events. Iloprost did not increase major adverse events such as myocardial infarction, cerebrovascular accident or death from any cause in the fortnight after the operation.

Commonly reported adverse events associated with iloprost in the Cochrane review and the perioperative RCT included pain at the infusion site, headache, flushing, nausea and vomiting, and hypotension.

Because intravenous iloprost is not licensed in the UK, there is no UK summary of product characteristics. An English translation of the Dutch summary of product characteristics for Ilomedin concentrate for infusion solution 0.1 mg/ml reports that very common adverse events (≥10% of people affected) associated with intravenous iloprost infusion include headache, flushing, nausea, vomiting and hyperhidrosis. These are reported to be most likely to occur during the initial dose titration to identify the optimal tolerable dose, and usually resolve with dose reduction. There may also be local infusion site reactions.

The more serious adverse drug reactions that have been observed in people receiving intravenous iloprost infusions include:

- hypotension, tachycardia, angina pectoris, and dyspnoea (common: occurring in between 1 in 10 and 1 in 100 people)
- cerebrovascular accident, myocardial infarction, pulmonary embolism, heart failure, convulsion, asthma, and pulmonary oedema. (uncommon: occurring in between 1 in 100 and 1 in 1000 people).

Reported contraindications to using iloprost infusion in the English translation of the Dutch summary of product characteristics for Ilomedin concentrate for infusion solution 0.1 mg/ml include conditions where the effect of iloprost on platelets might increase the risk of haemorrhage, severe coronary heart disease or unstable angina, myocardial infarction within the past 6 months, suspected decompensated left ventricular failure, serious arrhythmias, acute or chronic congestive heart failure (NYHA II-IV), pregnancy or lactation, or hypersensitivity to iloprost or the excipients included in the infusion solution.

Summaries of product characteristics or data sheet information for the product from different countries may differ slightly for example in the exact wording of the contraindications, and in the licensed indications for that country. The English translation of the Dutch summary of product
characteristics is not an approved UK regulatory document (Bayer: personal communication September 2013).

Cost effectiveness and cost

Because intravenous iloprost is unlicensed in the UK, no costs could be obtained from standard published sources or the manufacturer. Informal sources suggest that the cost is around £100 for a single 50 microgram ampoule, equating to around £3000 for a 4 week course. No cost-effectiveness analyses of intravenous iloprost in critical limb ischaemia were identified.

Relevance to NICE guidance programmes

The use of intravenous iloprost for critical limb ischaemia is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

There is NICE guidance on surgical and pain management of critical limb ischaemia in the guideline on Lower limb peripheral arterial disease: diagnosis and management (NICE clinical guideline 147). Other than drugs for pain management, this guideline does not make recommendations on medical alternatives for managing critical limb ischaemia.

Other NICE guidance also covers other conditions that can be relevant to critical limb ischaemia:

- **Diabetic foot problems: inpatient management of diabetic foot problems** (NICE clinical guideline 119) – includes recommendations on assessment of suspected limb ischaemia (the NICE clinical guideline on diabetic foot problems is currently being updated)

- **Type 2 diabetes foot problems: prevention and management of foot problems** (NICE clinical guideline 10) – mentions severe ischaemia as a consideration in management of foot ulcers (the NICE clinical guideline on diabetic foot problems is currently being updated)

- **Inadvertent perioperative hypothermia: the management of inadvertent perioperative hypothermia in adults** (NICE clinical guideline 65) – refers to critical limb ischaemia as a clinically urgent situation that might influence certain clinical decisions in managing perioperative hypothermia.

NICE has also issued guidance on a number of procedures and technologies that may be relevant for people with critical limb ischaemia or limb ischaemia more generally:
Intervention and alternatives

Iloprost is a synthetic analogue of prostacyclin. It is a vasodilator, and also has anti-inflammatory properties, reduces vascular permeability, and inhibits platelet function.

When used to treat critical limb ischaemia, iloprost is administered daily for 6 hours as an intravenous infusion through a peripheral vein or a central venous catheter. The dose is titrated up to the individual tolerance within a range of 0.5 to 2.0 nanograms/kg body weight/minute. Treatment duration is generally 4 weeks (English translation of the Dutch summary of product characteristics for Ilomedin concentrate for infusion solution 0.1 mg/ml).

Condition

Critical limb ischaemia is the end stage of peripheral arterial occlusive disease (PAOD), where macrovascular lesions cause such a reduction of distal perfusion pressure that microcirculation and nutrient blood flow to the tissues are severely disturbed (European Society for Vascular Surgery guideline for Critical Limb Ischaemia and Diabetic Foot, 2011). Critical limb ischaemia is characterised by ischaemic rest pain, ischaemic ulcers and/or gangrene. It can lead to gangrene, an increased risk of limb loss, and a marked increase in mortality (Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin, NICE technology appraisal guidance 159).

The European Society for Vascular Surgery guideline (2011) describes how the definition of critical limb ischaemia has changed over the years. The initial definition was based on clinical symptoms only. The European Society for Vascular Surgery guideline (2011) recommends that the presence of rest pain or a wound, ulcer or toe gangrene on a lower limb with arterial disease (PAOD) is not...
sufficient to qualify as critical limb ischaemia. These signs and symptoms must be recognised as attributable to the PAOD by combining specific clinical characteristics of pain and/or skin lesions, as well as other signs of severe chronic forefoot ischaemia, plus objective haemodynamic measurements. The guideline recommends using toe pressure measurement; although a threshold value for a diagnosis is not specified.

**Alternative treatment options**

The NICE clinical guideline on lower limb peripheral arterial disease recommends angioplasty or bypass surgery as options for people with critical limb ischaemia who require revascularisation, taking into account factors including:

- comorbidities
- pattern of disease
- availability of a vein
- patient preference.

NICE recommends that primary (bare metal) stent placement can be considered for some groups (those with critical limb ischaemia caused by complete aorto-iliac occlusion rather than stenosis) but not others (people with critical limb ischaemia caused by aorto-iliac disease, except complete occlusion, or femoro-popliteal disease). NICE also recommends that major amputation is not offered unless all options for revascularisation have been considered by a vascular multidisciplinary team.

Some people with critical limb ischaemia are reported to be poor candidates for revascularisation procedures, because of comorbidities or vascular anatomy (Ruffolo et al. 2010). These people only have medical treatments as alternatives to try to improve circulation. Amputation may be needed as a last resort.

Ruffolo et al (2010) describe that alternative treatments that have been considered for use include:

- drugs such as naftidrofuryl or pentoxifylline – these drugs are licensed for use in peripheral arterial disease in the UK but not specifically for use in critical limb ischaemia
- the prostanoids, such as iloprost, prostaglandin E1 (PGE1), and epoprostenol (prostacyclin or prostaglandin I2) – these drugs also do not have UK licences for treating critical limb ischaemia.
Evidence review: efficacy

Intravenous iloprost in people with critical limb ischaemia unsuitable for surgery

A Cochrane review by Ruffolo et al. (2010) was identified (search date 2009) that assessed using prostanoids (including iloprost) in people presenting with critical limb ischaemia who were unsuitable for rescue or reconstructive intervention. No subsequent randomised controlled trials (RCTs) in this population were identified in the literature search for this evidence summary. One previous meta-analysis was also identified (Loosemore et al. 1994) that assessed using iloprost for treating critical limb ischaemia in people who were unsuitable for rescue or reconstructive intervention. The Cochrane review assessed all of the studies entered in to Loosemore et al. (1994) but only a few studies were included in the Cochrane review after a strict methodological assessment. The Cochrane review included the following trials of intravenous iloprost:

- 5 RCTs (n=604) comparing intravenous iloprost with placebo
- 1 RCT (n=302) comparing different doses of intravenous iloprost
- 1 crossover RCT (n=36) comparing intravenous iloprost with prostaglandin E1 (PGE1, which is another prostanoid).

The Cochrane review identified 2 trials of oral iloprost, and 11 trials of other prostanoids; these are not discussed further here as they are not within the scope of the current evidence summary. The review included RCTs that were classified as being at moderate risk of bias; trials classified as high risk of bias were excluded. The RCTs comparing intravenous iloprost were all carried out in European countries (including 1 in the UK).

The populations included in the individual RCTs varied. Most studies included people with peripheral arterial occlusive disease (PAOD) stage III or IV (2 placebo-controlled RCTs and the 2 other intravenous iloprost RCTs). The other RCTs included hospitalised patients with PAOD at a critical ischaemic stage with or without diabetes mellitus (1 placebo-controlled RCT); people with 1 or more ischaemic ulcer (1 placebo-controlled RCT); or people with diabetes with ischaemic lesions (1 placebo-controlled RCT). Participants in the trial arms had average (mean or median) ages of between about 67 to 73 years.

In the placebo-controlled trials, iloprost was infused over a 6-hour period daily, for between 2 and 4 weeks. In the 3 RCTs for which the dose was reported in the review, the doses used were up to 2 nanograms/kg/min. The dose-comparison RCT used iloprost doses of 25, 50, 75 and...
100 micrograms infused over 6 hours daily for 4 weeks. The crossover RCT comparing iloprost with PGE1 focused on tolerability and infused each drug over a 3-hour period (doses not reported), with a day of washout between treatments.

When comparing iloprost with placebo, for each outcome assessed, only 3 out of the 5 RCTs provided data that could be pooled in the individual meta-analyses (each of the 5 RCTs contributed to at least 1 meta-analysis). In the meta-analyses of the primary outcomes, intravenous iloprost did not statistically significantly reduce total amputations compared with placebo at a mean follow-up of 21.3 weeks (total amputations included major [above/below the knee] and minor [partial amputation of the feet/fingers] amputations; 3 RCTs, n=318, risk ratio [RR] 0.79, 95% confidence interval [CI] 0.60 to 1.03). However, it statistically significantly reduced major amputations (defined as above/below the knee) at a mean follow-up of 21.3 weeks (3 RCTs, n=318, RR 0.69, 95% CI 0.52 to 0.93). Among the secondary outcomes, intravenous iloprost also statistically significantly improved ulcer healing (3 RCTs, n=367, RR 1.80, 95% CI 1.29 to 2.50) and rest-pain relief (3 RCTs, n=318, RR 1.54, 95% CI 1.19 to 1.99) at a mean follow-up of 14 to 14.7 weeks compared with placebo. (See table 1 for further details.) The review graded the quality of evidence as low for most of these outcomes, other than ulcer healing where quality was graded as very low.

Limited details were provided on the RCT with an active comparator (PGE1) and on the dose-comparison RCT. The results were described but no statistical analysis was performed. In the dose-comparison RCT (n=302), no significant intravenous iloprost dose response was reported for the outcomes of death, major amputations, ulcer healing or relief of rest pain (figures not reported). In the crossover RCT comparing 3-hour infusions of intravenous iloprost with intravenous PGE1 (n=36), a better patient profile regarding microcirculation was described for PGE1 (figures not reported). No clinical efficacy outcomes were reported.

The authors of the Cochrane review did not provide separate conclusions for iloprost alone, but the overall conclusion was that despite some positive results regarding rest-pain relief, ulcer healing and amputations, there was no conclusive evidence of the long-term effectiveness and safety of different prostanoids in people with critical limb ischaemia.

**Intravenous iloprost in people having surgery for critical limb ischaemia**

One multicenter double-blind RCT of perioperative iloprost in people having surgery for critical limb ischaemia was identified; it used both intravenous and intra-graft iloprost (IBISG 1996). Over a 2-year period, 528 people having femorodistal bypass surgery for critical limb ischaemia were randomised to iloprost or placebo. Eleven people (2.1%) were excluded after randomisation because they were unsuitable for bypass (n=8), or had treatment but had no data recorded (n=3).
Participant characteristics and results were reported for the remaining 517 people (267 randomised to iloprost and 250 randomised to placebo).

The trial took place in 21 vascular surgical centres in 6 countries in Northern Europe (including the UK and Ireland), with recruitment occurring between 1990 and 1992. It included people undergoing bypass surgery whose primary anastomosis was above the knee, and the distal anastomosis to the tibioperoneal trunk, anterior tibial, posterior tibial, or peroneal artery.

Critical limb ischaemia was defined as the presence of trophic lesions or persistent rest pain requiring analgesia for at least 2 weeks plus ankle pressure of less than 50 mmHg (except in people with diabetes with calcified arteries, where absence of palpable foot pulses was taken as evidence of severe vascular disease). All people in the study had severe lower limb ischaemia which was considered by the operating surgeons to be critical.

Almost all people had Fontaine stage III (pain in the extremities at rest, 34.0%) or Fontaine stage IV (necrosis and gangrene, 65.2%) peripheral arterial disease, with only 4 people (0.8%) not classified at these stages. Most people (96.5%) experienced pain at rest. More people in the iloprost group had both ulcers and necroses (31.8%) than in the placebo group (22%). There were also more women in the iloprost group (41.2%) than in the placebo group (36.0%). The statistical significance of these differences was not reported. Other than this, the authors reported the groups as generally well matched. The mean age of people in the study was 71.2 years.

Most of the surgeries used vein grafts (82%, including composite grafts), with the remainder using prosthetic or composite vein-prosthetic grafts (18%). More people in the iloprost group had prosthetic graft surgery (21.3%) than in the placebo group (14.0%; significance of difference not reported). Minimum graft diameters were reported to be significantly smaller in the iloprost group (3.71±1.02) than in the placebo group (4.00±1.39; units and p value not reported). Concomitant procedures (endarterectomy or profundaplasty) were reported to be performed in similar numbers in each group. Use of antithrombotic drugs after surgery was reported not to differ significantly between the groups, but use of aspirin and dextran stents were higher in the placebo group (aspirin: 25.1% with iloprost compared with 30.8% with placebo; dextran: 25.1% with iloprost compared with 31.2% with placebo).

Iloprost (or placebo) was diluted with 500 ml physiological saline and given as:

- an intravenous infusion for 1 hour after induction of anaesthesia at a rate of up to 20 ml/hour (equivalent in the average patient to about 1.0 nanograms/kg/minute of iloprost in the iloprost group, 97.9% of people received either iloprost or placebo)
followed by an intra-graft injection of 15 ml (equivalent to 3000 nanograms of iloprost in the iloprost group) into the proximal end of the bypass graft on completion of the procedure but before skin closure (96.4% of people received either iloprost or placebo)

followed by three intravenous infusions lasting 6 hours; the first at a rate of up to 20 ml/hour (equivalent in the average patient to about 1.0 nanograms/kg/minute of iloprost in the iloprost group) starting 1 hour after the end of the operation, and the remaining infusions on the 2 days following the operation at a rate of up to 40 ml/hour (equivalent in the average patient to about 2.0 nanograms/kg/minute of iloprost in the iloprost group; 83.1% of people in the iloprost group, and 84.8% of people in the placebo group, received all 3 infusions).

Primary patency was the outcome on which the power calculation for the study was based. It was defined as patency of the graft without any further intervention after skin closure in the initial bypass operation. If the graft occluded and intervention was successful, this was referred to as secondary patency. Patency was analysed separately for vein grafts and those grafts that contained prosthetic material (either the whole or part of the graft). The study had 90% power to detect a 13% increase in primary patency of vein grafts with iloprost compared with placebo (from 75% to 88%), at the 0.05 level of significance.

Over 12 months there was no statistically significant difference between iloprost and placebo in the primary patency of the grafts (displayed graphically, figures not reported; vein grafts p=0.81, prosthetic grafts p=0.49). Over 12 months there was also no statistically significant difference between the groups in the secondary patency of the grafts (figures not reported; vein grafts p=0.42, prosthetic grafts p=0.77).

Although differences between iloprost and placebo in graft patency were non-significant at 12 months, the difference between iloprost and placebo was larger for prosthetic grafts than vein grafts. For prosthetic grafts, people who received iloprost showed statistically significantly higher graft patencies at the end of the 3 days of treatment than with placebo (primary patency: 94.5% compared with 74.3%, p<0.01), but this difference was not maintained over the 12 months of follow-up (primary patency p=0.49; secondary patency p=0.77). The authors suggested that this might have been due to the short length of iloprost treatment and the relatively small number of prosthetic grafts used. They also note that vein graft diameter, female sex, and aspirin use were statistically associated with graft patency, and their distribution favoured the placebo group, but not significantly so.

Over 12 months there was no statistically significant difference between vein grafts and prosthetic grafts in primary patency rates (p=0.25), but there was a statistically significant difference in secondary patency rates in favour of vein grafts (p=0.047). Given that more people in the iloprost
group had prosthetic graft surgery than in the placebo group, this difference in graft performance may have influenced between-group differences.

Some type of surgical intervention on the affected limb (other than amputation) was received by about a third of people in both groups (31.6% with iloprost compared with 31.2% with placebo). Local thrombolytic treatment was used in 2.9% of people who received iloprost and 5.1% of those who received placebo.

There was no significant difference in amputation rates between the treatment groups over 12 months (displayed graphically by graft type, figures not reported; p=0.71 in people with vein grafts, p=0.78 in people with prosthetic grafts). Overall limb salvage rates at 12 months were 81.1% for vein grafts (81.8% with iloprost compared with 80.5% with placebo), and 72.8% with prosthetic grafts (73.7% with iloprost compared with 71.4% with placebo). Clinical status (Fontaine stage) was reported to not be statistically significantly different between treatment groups at 12 months (figures not reported by group). Overall, at the end of 12 months, 46.0% of participants were Fontaine stage I or II, 15.1% remained at stage III or IV, 20.3% had had an amputation, 16.4% had died, and the status of 2.2% was not known.

Evidence review: safety

Meta-analysis in the systematic review by Ruffolo et al. (2010) found that about twice as many people experienced adverse events with intravenous iloprost compared with placebo (3 RCTs, n=378; RR 2.05, 95% CI 1.68 to 2.49). It reported that the most frequent adverse events with intravenous iloprost were headache, flushing, nausea and vomiting. The dose-comparison RCT included in the review found that adverse events showed a statistically significant dose response (p<0.001). In the RCT of intravenous perioperative iloprost in people with critical limb ischaemia undergoing femorodistal bypass grafting surgery (IBISG 1996), significantly more people receiving iloprost experienced intra-operative adverse events than those receiving placebo (figures not reported). The intra-operative adverse events were mainly hypotension (14.6% with iloprost compared with 4.0% with placebo; p<0.001). There were no significant differences in other intra-operative adverse events. Statistically significantly more people receiving iloprost also experienced post-operative adverse events than those receiving placebo (57.7% compared with 37.2%; p<0.001). However, discontinuation rates did not differ between the groups (figures not reported). Post-operatively, hypotension, nausea, headache, flushing and injection site reactions were more common with iloprost than placebo (figures not reported). There was no significant difference between the groups in major adverse events in the fortnight after the operation (rates with iloprost compared with placebo: myocardial infarction: 3.7% compared with 4.4%; cerebrovascular
accident: 1.1% compared with 0.8%; death from any cause: 3.4% compared with 2.4% respectively; p values not reported).

Because intravenous iloprost is not licensed in the UK there is no UK summary of product characteristics. An English translation of the Dutch summary of product characteristics for Ilomedin concentrate for infusion solution 0.1 mg/ml reports that the very common adverse events (≥10% of people affected) associated with intravenous iloprost infusion include headache, flushing, nausea, vomiting and hyperhidrosis. These are reported to be most likely to occur during the initial dose titration to identify the optimal tolerable dose, and usually resolve with dose reduction. There may also be local infusion site reactions.

The more serious adverse events that have been observed in people receiving intravenous iloprost infusions include:

- hypotension, tachycardia, angina pectoris, and dyspnoea (common: occurring in between 1 in 10 and 1 in 100 people)

- cerebrovascular accident, myocardial infarction, pulmonary embolism, heart failure, convulsion, asthma, and pulmonary oedema. (uncommon: occurring in between 1 in 100 and 1 in 1000 people).

Reported contraindications to using intravenous iloprost infusion in the English translation of the Dutch summary of product characteristics for Ilomedin concentrate for infusion solution 0.1 mg/ml include:

- conditions where the effect of iloprost on platelets might increase the risk of haemorrhage (for example, active peptic ulcers, trauma, or intracranial haemorrhage)

- severe coronary heart disease or unstable angina

- myocardial infarction within the past 6 months

- suspected decompensated left ventricular failure

- serious arrhythmias

- acute or chronic congestive heart failure (NYHA II-IV)

- pregnancy or lactation

- hypersensitivity to iloprost or the excipients included in the infusion solution.
Summaries of product characteristics and data sheet information for the product from different countries may differ slightly in the exact wording of the contraindications, and in the licensed indications for that country. The English translation of the Dutch summary of product characteristics is not an approved UK regulatory document (Bayer: personal communication September 2013).

**Evidence review: economic issues**

**Cost effectiveness**

No studies assessing the cost effectiveness of intravenous iloprost for critical limb ischaemia were identified.

**Cost**

Because intravenous iloprost is unlicensed in the UK, no costs could be obtained from standard published sources or the manufacturer. Informal sources suggest that the cost is around £100 for a single 50 microgram ampoule, equating to around £3000 for a 4 week course.

**Current drug usage**

No data on current use of intravenous iloprost for critical limb ischaemia in the UK were identified, therefore current usage is unclear.

**Evidence strengths and limitations**

This summary is based on evidence from a Cochrane review of prostanoids for critical limb ischaemia (Ruffolo et al. 2010), and a randomised controlled trial (RCT) of intravenous perioperative iloprost in people with critical limb ischaemia undergoing femorodistal bypass grafting surgery (IBISG 1996).

The Cochrane review included 7 RCTs assessing intravenous iloprost. The review excluded RCTs that were rated as being at a high risk of bias (at least 3 specified quality criteria judged as inadequate) or of low quality (Jadad score of 0). Most commonly, trials were excluded for lack of blinding, withdrawal of 10% or more of the study population, lack of intention-to-treat analysis, or treatment differing between groups. Despite this, the included trials were all assessed as being at moderate risk of bias (1 or more specified quality criteria partly met and 2 or fewer criteria inadequate).
The quality of the evidence that provided the meta-analysed outcomes comparing intravenous iloprost with placebo was assessed as either low or very low using the GRADE approach. The 'low quality evidence' grading indicates that further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. The 'very low quality evidence' grading indicates that the estimate of effect is very uncertain.

The doses used in the dose-response RCT were not described in terms of nanograms/kg/minute, but as micrograms. This makes the results difficult to compare with the standard dose range of 0.5 to 2.0 nanograms/kg/minute. The crossover RCT comparing intravenous iloprost with prostaglandin E1 (PGE1) was small (n=36) and did not report clinical efficacy outcomes.

Most of the trials of intravenous iloprost included in the review were carried out in the 1990s (6 RCTs), and the most recent was a trial comparing intravenous iloprost with PGE1, which was carried out in 2003. The RCT of perioperative iloprost was published in 1996. Clinical practice is likely to have changed over time, and therefore results may be less applicable to current practice. For example, different definitions of critical limb ischaemia have been used over time; therefore results of early RCTs may be less generalisable to populations defined as having critical limb ischaemia in present times. The review did not provide details of whether the RCTs used haemodynamic measurements as part of the diagnosis of critical limb ischaemia, and these measurements are recommended as part of current diagnosis. The studies in the review included slightly different populations (for example, peripheral arterial occlusive disease [PAOD] stage III or IV, or people with ischaemic lesions). In addition, advances in surgical capabilities may mean that the group described as unsuitable for surgery may have changed since the RCTs included in the review were performed.

The RCT of perioperative iloprost did use haemodynamic measurement as part of diagnosis, but noted that almost half of its participants would not have met the European consensus definition of critical limb ischaemia in place at the time (IBISG 1996). All people in the study had severe limb ischaemia and were considered by the operating surgeons to be critical. This RCT used only a relatively short course of iloprost treatment (3 days) compared with the RCTs that included people whose condition was not suitable for surgery (2 to 4 weeks).

In the RCT of perioperative iloprost, although analyses were reported to be by intention to treat, they only included those for whom graft patency could be assessed. The analyses didn't include 11 people (2.1%) who were excluded after randomisation, 8 of whom were found to be unsuitable for bypass operation after starting the procedure, and 3 of whom had treatment but no data had been recorded. Follow-up was high, with data at 12 months being reported for 97.8% of participants.
Details of how randomisation was carried out in the trial were not reported, and it was not clear if allocation was concealed. The study was reported to be double blind, but no further details were provided about who was blinded or how successful blinding was. The adverse events associated with iloprost (for example, flushing, headache and nausea) may have meant that participants or those treating them could guess that iloprost was being received.

There were imbalances between the groups in factors that were found to be associated with graft patency (gender, graft minimum diameter, and aspirin use); although these were not significant, they could favour placebo. The iloprost group also received more prosthetic grafts, which tended to show lower patency rates, although the difference was not significant.

The main outcome assessed by the perioperative iloprost trial was graft patency. This was not considered to be a good surrogate outcome by the Guideline Development Group for the NICE clinical guideline on lower limb peripheral arterial disease. This was mainly because of a lack of clear evidence of a link between patency and clinical outcomes of relevance to patients (for example, symptoms, quality of life or need for further intervention). Different definitions of patency are also used in the literature.

Data collection in the RCT was independently monitored by a coordinating centre and validated by reference to original sources such as hospital records, which should increase reliability of outcome collection.

Summary for patients

A summary written for patients is available on the NICE website.

References

Bayer B.V. (2012) Ilomedin, concentrate for infusion solution 0.1 mg/ml summary of product characteristics (English translation)

Bayer plc (2013) Ventavis 10 microgram/ml nebuliser solution summary of product characteristics [online; accessed 11 October 2013]


National Institute of Health and Clinical Excellence (2008) Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. NICE technology appraisal guidance 159

National Institute of Health and Clinical Excellence (2012) Lower limb peripheral arterial disease: diagnosis and management. NICE clinical guideline 147

National Institute of Health and Clinical Excellence (2012) Percutaneous laser atherectomy as an adjunct to balloon angioplasty (with or without stenting) for peripheral arterial disease. NICE interventional procedures guidance 433


Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

Project team

Bazian Ltd

Medicines and Prescribing Centre, NICE

Peer reviewers and contributors

Lizzie Amis, Senior Public Involvement Adviser, Public Involvement Programme, NICE
Expert advisers

Mr J Vince Smyth, Consultant Vascular and Endovascular Surgeon, Manchester Royal Infirmary

Mr Mike Wyatt, Honorary Secretary, The Vascular Society, London

Ariane Herrick, Professor of Rheumatology, University of Manchester, and Honorary Consultant Rheumatologist, Salford Royal NHS Foundation Trust

Declarations of interest

No relevant interests declared.

Appendix: Search strategy and evidence selection

Search strategy

- General background, guidelines and technology assessments:
  - Broad internet search: Google e.g.: ventavis OR iloprost OR ilomedine "critical limb ischaemia" filetype:pdf
  - Trip Database

MEDLINE (via Ovid)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1 iloprost/ (1941)
2 (iloprost or ilomedine or ventavis).tw. (2265)
3 1 or 2 (2644)
4 Ischemia/ (43208)

5 ((leg or limb) adj3 (hypoperfusion or isch?emia)).tw. (6524)

6 4 or 5 (45613)

7 3 and 6 (171)

8 limit 7 to english language (127)

Embase (via Ovid) Database:

Embase <1988 to 2013 September 10>

Search Strategy:

--------------------------------------------------------------------------------

1 Iloprost/ (5333)

2 (iloprost or ilomedine or ventavis).tw. (2875)

3 1 or 2 (5568)

4 *Ischemia/ (15245)

5 ((leg or limb) adj3 (hypoperfusion or isch?emia)).tw. (8248)

6 4 or 5 (22517)

7 3 and 6 (223)

8 limit 7 to english language (167)

9 limit 8 to exclude medline journals (18)

Cochrane Central Register of Controlled Trials (CENTRAL)

#1 limb near isch*emia:ti,ab,kw (Word variations have been searched) 440
Critical limb ischaemia in peripheral vascular disease: intravenous iloprost (ESUOM24)

#2 leg near isch*emia:ti,ab,kw 388

#3 #1 or #2 679

#4 iloprost or ventavis or ilomedine:ti,ab,kw 310

#5 #3 and #4 in Trials 34

CRD HTA, DARE and EED database

1 (iloprost or ventavis or ilomedine) 27

2 (isch*emia) 732

3 #1 AND #2 6

Grey literature and ongoing trials

- NICE Evidence
- Health Canada – Clinical Trials Search
- ClinicalTrials.gov

Manufacturers' websites

- Bayer plc

Evidence selection

Systematic reviews of randomised controlled trials (RCTs) and individual RCTs assessing the effects of intravenous iloprost for treating critical limb ischaemia were included. Trials that assessed combined intravenous iloprost plus intra-graft iloprost for treating critical limb ischaemia were also included. Studies assessing other routes of iloprost delivery (for example, oral and nebulised routes) for critical limb ischaemia were not included.

Where more than 1 systematic review assessing the same question was available, the most recent was selected for inclusion. Because a good-quality systematic review of iloprost for treating critical limb ischaemia that was unsuitable for surgery was identified and included, only RCTs of iloprost in
a non-surgically treated population published subsequent to the review's search date (2009) were considered for inclusion. No such subsequent RCTs in this population were identified.

Non-RCT studies were excluded, as were studies that did not assess clinical outcomes (for example, studies that assessed only surrogate outcomes such as biochemical or cell-based outcomes).

About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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