Iloprost infusion for the Management of Severe Symptomatic Peripheral Ischaemia in patients with Secondary Raynaud’s Disease or Systemic Scleroderma to prevent Limb Amputation
VERSION CONTROL

Document Location

This document is only valid on the day it was printed.

The current version of this document will be found at www.shropshireccg.nhs.uk/policies

Revision History

Date of this revision: First draft - March 2014

Date of next revision: March 2017 unless required sooner

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<tr>
<th>Version</th>
<th>Date</th>
<th>Author</th>
<th>Change Description</th>
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<tr>
<td>1.0</td>
<td>March 2014</td>
<td>Trish Campbell</td>
<td></td>
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Approvals

This document requires the following approvals:

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<tr>
<th>Name / Committee</th>
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<tr>
<td>Clinical Assurance Panel (CAP)</td>
<td></td>
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<tr>
<td>Trish Campbell</td>
<td>Head of Medicines Management, Clinical Quality and Safety</td>
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Distribution

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<tr>
<td>Published to CCG website</td>
<td>02.06.14</td>
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Policy on Iloprost Infusion for the Management of Severe Symptomatic Peripheral Ischaemia in Patients with Secondary Raynaud’s Disease or Systemic Scleroderma to Prevent Limb Amputation

Purpose:
The purpose of this policy is to provide Iloprost infusion to patients with Secondary Raynaud’s Disease (SRD) or Systemic Scleroderma who meet the criteria set out in this policy.

Policy statement:
Patients with Secondary Raynaud’s Disease or Systemic Scleroderma may be treated with Iloprost for the prevention of ischaemic pain, peripheral ulcers, necrosis of toes and fingers in order to prevent patients proceeding to amputation and the associated surgical and treatment costs associated with this.

Iloprost is not currently licensed in the UK for treatment of SRD and should only be given under the direction of a consultant in secondary care.

Patients must meet the starting criteria and be aware that treatment will be stopped if the stopping criteria are met.

Place in therapy:
Patients receiving Iloprost will have SRD with severe symptomatic ischaemia due to vasospasm and resultant decrease in blood flow. Before Iloprost is considered patients must already have been tried on optimal medical therapy for the prevention of vasospasm (calcium antagonists, alpha antagonists, possibly Naftidrofuryl oxalate) and Bosentan. Bosentan is the only agent indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

Secondary RP is suggested by age of onset greater than 30 years; episodes that are intense, painful, asymmetric, or associated with ischaemic skin lesions; concomitant symptoms suggestive of a connective tissue disease; specific autoantibodies; and evidence of microvascular disease on microscopy of nail-fold capillaries.

Primary RP is characterized by symmetric attacks; the absence of tissue necrosis, ulceration, or gangrene; the absence of a secondary cause; normal nail-fold capillaries; a negative test for antinuclear antibody; and a normal erythrocyte sedimentation rate. Symptoms are generally mild, and age of onset is generally younger than 30 years

Starting Criteria for Iloprost:
- Consultant initiation only.
• Patient has severe ischaemic pain, digit/toe necrosis or gangrene.
• Patient is already on optimal medical therapy for the management of Raynaud’s/Systemic Scleroderma and still has symptomatic peripheral ischaemia.
• Patient is at very high risk of digit/toe amputation.
• Patient has no contraindications to Iloprost.

Stopping Criteria:
• Patient is not responding / poorly responding to Iloprost after first course.
• Patient develops a severe adverse drug effect to Iloprost necessitating discontinuation.
• Patient is non-concordant with arriving to hospital for Iloprost infusion.
• Patient has a change in underlying condition that means Iloprost therapy is no longer appropriate.

Background:
Raynaud’s phenomenon (RP) is described as episodic digital ischemic vasospasm triggered by cold- or emotional-stress leading to a pale and cyanotic skin with a post-ischemic phase of hyperemia. It most commonly affects the fingers. RP occurs as a result of vasoconstriction of the digital arteries, precapillary arterioles, and cutaneous arteriovenous shunts. Secondary RP most often occurs in the context of a connective tissue disease, of which systemic sclerosis (SSc) is the most recognised association, and occurs in 90% of patients with SSc.

Systemic sclerosis is a multisystem autoimmune disease in which there is increased fibroblast activity resulting in abnormal growth of connective tissue. This causes vascular damage and fibrosis. Fibrosis occurs in skin, the gastrointestinal (GI) tract and other internal organs. SSc develops in approximately 2 people per 100,000 each year. Therefore approximately 6 people could be expected to present with the condition each year in Shropshire and 4 in NHS T&W, although only a minority will have the severest form of the condition.

Patients receiving Iloprost will need admission into hospital for a series of five continuous intravenous infusions, at a dose titrated according to patient response, given over a number of hours on 5 consecutive days; analgesia for management of Iloprost-induced headache; monitoring of blood pressure and advice on appropriateness of taking specific anti-hypertensives prior to and post infusion. They will also need assessment in out-patients for any improvement in consequence of peripheral ischaemia.

Side effects:
The most common side effects are facial flushing and headache. Other effects are malaise, nausea, vomiting, abdominal pain, diarrhoea, sweating, pain in the affected limb, paraesthesia, fever, chill, confusion, apathy, sedation,
agitation, lowering or increase of blood pressure, tachycardia and arrhythmias.

**Interactions:**
Iloprost increases the risk of bleeding when administered with antiplatelets, and may increase bleeding risk with coumarins and heparin. Iloprost may have an additive effect on the antihypertensive activity of β-blockers, calcium-channel blockers, vasodilators and ACE inhibitors. If significant hypotension occurs, this can be corrected by reducing the dose of Iloprost and administering intravenous fluids.

**Clinical efficacy:**
There have been a number of studies regarding the use of the prostacyclin analogue, Iloprost, in systemic sclerosis and Raynaud's phenomenon. A 2011 systematic review found that there was clear evidence in favour of IV Iloprost to treat secondary RP.

A Cochrane review by Pope et al in 2009 reported on Iloprost (intravenous (IV) and oral) in patients with RP secondary to systemic sclerosis. Seven RCTs were included (n=332). One RCT studied oral cisaprost, and the remainder examined (oral or IV) Iloprost. In the studies comparing Iloprost with the placebo, the (short-term) change from baseline in severity of attacks yielded a WMD of -0.69 (95% CI, -1.12 to -0.26), which was significant in favour of Iloprost. Treatment with IV Iloprost resulted in significantly higher improvements than the placebo (odds ratio [OR] 2.61; 95% CI, 1.27–5.38). It reported that IV Iloprost was effective in the treatment of RP secondary to scleroderma at decreasing the frequency and severity of attacks and preventing or healing digital ulcers, and that the effect seemed to be prolonged after the intravenous infusion is given.

A 1994 RCT by Wigley et al found that the mean weekly number of Raynaud attacks decreased 39.1% with Iloprost and 22.2% with placebo (P = 0.005). In addition, the mean percentage of improvement in a global Raynaud severity score during the entire 9-week follow-up was greater in patients given Iloprost (34.8%) than in those receiving placebo (19.7%) (P = 0.011). The physician's overall rating of treatment effect showed greater improvement with Iloprost than with placebo at week 6 (52.4% compared with 27.4%; P = 0.008) and week 9 (60.9% compared with 26.9%; P < 0.001). At week 3, 14.6% more patients receiving Iloprost had 50% or more lesions heal compared with those given placebo (95% CI, 0.9% to 30%). During the infusion, 59 (92%) of the patients receiving Iloprost had one or more side effects compared with 38 (57%) of the patients receiving placebo. The authors concluded that Iloprost is effective for the short-term palliation of severe Raynaud phenomenon in patients with systemic sclerosis.

The EULAR (European League Against Rheumatism) Scleroderma Trials and Research Group guidelines (2009) state that IV Iloprost should be considered for severe systemic sclerosis-related Raynaud's phenomenon attacks. They state that intravenous Iloprost is efficacious in healing digital
ulcers in patients with systemic sclerosis and should be considered in the
treatment of active digital ulcers.

BMJ Best Practice® (BMJ Best Practice, 2013) indicates Iloprost second line
(after endothelin receptor antagonists) for systemic sclerosis and Raynaud's
phenomenon with digital ulcer development.

References

i Effectiveness of interventions for secondary Raynaud's phenomenon: a
systematic review. Huisstede BM, Hoogvliet P, Paulis WD, van Middelkoop M,
Jul;92(7):1166-80.

ii Cochrane Intervention Review: Iloprost and cisaprost for Raynaud’s
phenomenon in progressive systemic sclerosis. Pope J, Fenlon D, Thompson
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000953/abstract -
Accessed 22/11/13

iii Intravenous Iloprost treatment of Raynaud’s phenomenon and ischemic
ulcers secondary to systemic sclerosis. Wigley FM, Seibold JR, Wise RA,

iv EULAR recommendations for the treatment of systemic sclerosis: a report
from the EULAR Scleroderma Trials and Research group (EUSTAR)

v Systemic Sclerosis (Scleroderma) – Treatment Options. BMJ Best Practice,
updated August 2013 (Accessed 26/11/13) Available from:
Implementation of Guidance issued by the National Institute for Health and Clinical Excellence (NICE)

Policy on Iloprost Infusion for the Management of Severe Symptomatic Peripheral Ischaemia in Patients with Secondary Raynaud’s Disease or Systemic Scleroderma to Prevent Limb Amputation.

To ensure that the Trust is reimbursed for this drug, the following template must be completed and forwarded to the commissioning CCG.

**Policy statement:**
Patients with Secondary Raynaud’s Disease or Systemic Scleroderma may be treated with Iloprost for the prevention of ischaemic pain, peripheral ulcers, necrosis of toes and fingers in order to prevent patients proceeding to amputation and the associated surgical and treatment costs associated with this. Iloprost is not currently licensed in the UK for treatment of SRD and should only be given under the direction of a consultant in secondary care. Patients must meet the starting criteria and be aware that treatment will be stopped if the stopping criteria are met.

**Place in therapy:**
Patients receiving Iloprost will have SRD with severe symptomatic ischaemia due to vasospasm and resultant decrease in blood flow. Before Iloprost is considered patients must already have been tried on optimal medical therapy for the prevention of vasospasm such as calcium antagonists, alpha antagonists, possibly Naftidrofuryl oxalate. Bosentan is not a CCG responsible drug and if consultants wish to prescribe it they must apply through the IFR route to NHS England. GPs Must NOT be asked to prescribe Bosentan for any clinical indication. Any requests to GPs to prescribe Bosentan will be recharged to the Trust and followed up through the Clinical Quality Review Meetings with the Trust.
SRD is suggested by age of onset greater than 30 years; episodes that are intense, painful, asymmetric, or associated with ischaemic skin lesions; concomitant symptoms suggestive of a connective tissue disease; specific autoantibodies; and evidence of microvascular disease on microscopy of nail-fold capillaries.

**Starting Criteria for Iloprost:**
- Consultant initiation only.
- Patient has severe ischaemic pain, digit/toe necrosis or gangrene.
- Patient is already on optimal medical therapy for the management of Raynaud’s/Systemic Scleroderma and still has symptomatic peripheral ischaemia.
- Patient is at very high risk of digit/toe amputation.
- Patient has no contraindications to Iloprost.

**Stopping Criteria:**
- Patient is not responding / poorly responding to Iloprost after first course.
- Patient develops a severe adverse drug effect to Iloprost necessitating discontinuation.
- Patient is non-concordant with arriving to hospital for Iloprost infusion.
- Patient has a change in underlying condition that means Iloprost therapy is no longer appropriate.
To be completed by a rheumatology consultant or specialist registrar:

Patient’s initials: __________________________  Date of Birth: __________

NHS number (must be provided): ______________________________________

NHS Trust: __________________________________________________________

Contact name/address: _______________________________________________

Telephone: __________________________________________________________

Consultant: __________________________________________________________

<table>
<thead>
<tr>
<th>1. Does the patient have severe ischaemic pain, digit/toe necrosis or gangrene?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Is the patient already on optimal medical therapy for the management of Raynaud's/Systemic Scleroderma and still have symptomatic peripheral ischaemia?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3. Patient is at very high risk of digit/toe amputation?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4. Does the patient have any contraindications to Iloprost?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**Consultant/SpR signature:**

**Print Consultant/SpR name:**

**Date:**

Please forward this template to:-

Trish Campbell
Head of Medicines Management Clinical Quality and Safety
Shropshire County CCG
William Farr House
Myston Oak Road
Shrewsbury
SY3 8XL
Telephone: 01743 277557
E-mail: med.safety@nhs.net