

1. Introduction and Who Guideline applies to

Raynaud's phenomenon is an exaggerated vascular response to cold temperatures or emotional stimuli. Primary Raynaud's (also known as idiopathic) phenomenon is common in younger age groups, particularly women, and is not associated with an underlying connective tissue disorder such as Systemic Lupus Erythematosus (SLE) or Systemic Sclerosis (SS).

Secondary Raynaud's phenomenon is associated with connective tissue disorders such as SLE and SS. Digital ischaemia and ulceration is more common in this group and can result in significant morbidity related to pain and tissue loss.

Sildenafil, iloprost and bosentan are commissioned by NHS England (NHSE)¹ and endorsed by both the British Society of Rheumatology (BSR)² and the European League Against Rheumatism (EULAR)³ guidelines for use in patients with severe, refractory or multiple digital ulceration due to SS that has failed to respond to standard therapies.

2. Guideline Standards and Procedures

Summary Flow Chart.



- *Nifedipine suggested first line CCB.
- **Losartan suggested first line ARB.
- ***May be used first line if there are supply/clinical issues around prescription of first line drugs, or at clinical discretion.
- Patients will have at least 6 weeks of standard medical treatment and 6 weeks of sildenafil before moving on to IV Prostanoid. However, in cases of worsening active DU, patients may require escalation to IV Prostanoid earlier in order to save the digit.
- Patients who fail IV Prostanoid plus sildenafil, or who require more than 3 infusions of iloprost within 12 months should receive bosentan.
- **This document summarises use of Iloprost.**

Iloprost

Prescribing

To be prescribed using the iloprost prescription chart (see Appendix 2) and EPMA if the patient is an inpatient.

Baseline blood tests (full blood count, renal and liver function) should be no more than four weeks old at date of administration

Pre-administration

Patient should be weighed to determine dosage.
 Ensure patient has a care plan and instructions are followed.
 Baseline blood pressure and pulse to be recorded. Do not administer if systolic blood pressure less than 90mmHg.

Dosing

Given via intravenous infusion over 3-7 days, with usual course length of 5 days (Can be repeated in 6-8 weeks if ongoing activity of digital ulcer).
 Dosing 0.5-2 nanogram/kg/min given over maximum of 6 hours. Dosing commenced at 0.5nanogram/kg/min then increased by 0.5 nanogram/kg/min increments every 30 minutes to maximum 2 nanogram/kg/min if tolerated (see chart below)

Dose of iloprost (ng/kg/min)	Weight of patient (kg)										
	Flow rates mls/hour										
	40	45	50	55	60	65	70	75	80	85	90
0.5	0.6	0.7	0.8	0.8	0.9	1.0	1.1	1.1	1.2	1.3	1.3
1.0	1.2	1.3	1.5	1.6	1.8	2.0	2.1	2.2	2.4	2.5	2.7
1.5	1.8	2.0	2.2	2.5	2.7	2.9	3.2	3.4	3.6	3.8	4.0
2.0	2.4	2.7	3.0	3.3	3.6	3.9	4.2	4.5	4.8	5.1	5.4

If a reduction in dosage is required this should be in increments of 0.5 nanogram/kg/min.
 Dosing rates should be documented on drug infusion chart (see appendix).

Administration

To be administered using an electronic infusion device via central or peripheral line.
 Dilute in sodium chloride 0.9% or glucose 5%.
 For patients <80kg: 50micrograms (0.5mL) diluted to 25mL
 For patients >80kg: 100micrograms (1mL) diluted to 50mL
 Resultant strength is 2micrograms/mL
 Monitor blood pressure and pulse at initiation and at least every 30 minutes during Administration (provided on treatment chart)
 Lying and standing blood pressure should also be 1 hour after completion to check for postural hypotension.
 Patients should remain in lying or seated position during the infusion to minimise risk of postural hypotension.
 The cannula should not be flushed following completion of treatment. After the infusion is stopped, disconnect the administration set, aspirate the cannula contents and then flush with sodium chloride 0.9%.
 During infusions the cannulated site should be observed for pain, swelling or redness. If this occurs, in consultation with the doctor, the infusion may be stopped and a fresh cannula may need to be inserted. The patient should be encouraged to inform the nurse of any pain or swelling at the cannulated site or of any other side effects.

Cautions

Concomitant vasodilators/antihypertensives

Oral vasodilators/antihypertensives are generally discontinued for duration of infusion course. If there is doubt, the patient should not take them but bring them to the infusion appointment to discuss with the clinician/nurse.

Contra-indications:

- Conditions that increase the risk of haemorrhage
- Congenital or acquired valvular defects of the myocardium
- Decompensated heart failure
- Severe coronary heart disease
- Unstable angina
- Stroke within 3 months
- Myocardial infarction within 6 months

Pregnancy & breast feeding:

- Manufacturer advises to avoid – teratogenic in animal studies

Monitoring

Potential adverse effects are dose related. The infusion should be ceased if any of following occur.

- Hypotension
- Tachycardia
- Flushing
- Headache

Infusion can be recommenced at previously tolerated dose after an hour if normalised.

Other potential adverse effects include:

- Bradycardia with pallor
- Sweating
- Nausea and vomiting
- Abdominal discomfort
- Erythema over infusion site
- Jaw pain or non-specific musculoskeletal pain
- Anxiety
- Flu-like symptoms
- Hyperglycaemia
- Drowsiness
- Chest pain
- Syncope

Supply

Local arrangement.

Appendix 1

Evidence

A systematic review and meta-analysis involving 332 patients in seven randomized trials showed benefit in patients with secondary RP associated with systemic sclerosis, with evidence for decreasing the severity and frequency of acute attacks and for preventing or healing digital ulcers (1). Dosing regimens in the trials varied. The effect was prolonged beyond the period of the infusion, and limited data suggested that the IV preparation was more effective than oral iloprost.

- The range of findings and approaches are illustrated by the following:
A randomized trial involving 131 patients with secondary RP associated with SSc, which showed the efficacy of iloprost given intravenously (0.5 to 2 ng/kg per minute for six hours on five successive days) compared with placebo (2). Iloprost use resulted in short-term palliation of severe RP. The mean weekly attack rate and the Raynaud severity score both decreased in the patients treated with iloprost compared with those receiving placebo (39 and 35 percent versus 22 and 20 percent, respectively).
Adverse events were seen in significantly more patients treated with iloprost compared with those receiving placebo (92 versus 57 percent). The most common side effects included headache (54 versus 21 percent), flushing (32 versus 6 percent), and nausea (29 versus 11 percent). Jaw pain, diarrhoea, vomiting, injection site reactions, and myalgia were also common (5 to 15 percent versus 0 to 2 percent). The side effects were reversed by decreasing the dose of the iloprost and the rate of infusion. Hypotension and rashes may also occur. Withdrawal from the trial, usually for lack of benefit, was similar in the two groups (13 percent).
- A study that found short-term infusions of IV iloprost (for eight hours/day on three consecutive days, with a repeat infusion for one day on week eight) comparably effective to oral nifedipine (up to 60 mg/day as tolerated for 16 weeks) in secondary RP associated with SSc (3)
- The use of iloprost in 30 patients with SSc with maintenance infusions every three weeks for a median of three years following an initial cycle of infusions over five days (4) Healing of digital ulcers and a subjective decrease RP were reported in this long-term uncontrolled study.

Protocols for the intravenous administration of iloprost

- Before starting the infusion, check the patient's pulse and blood pressure and record this on the drug chart
- All patients should commence the first iloprost infusion of each treatment period at 1 mL/hour
- Follow the guidance below for infusion rates for specific patient groups
- Check the patient's pulse and blood pressure 30 minutes after starting the infusion and then every 30 minutes after any increase in the infusion rate.

Intermittent Infusion Protocol (Daily 6 hour Infusions)

Iloprost should be administered for a maximum of 6 hours per day for a maximum of 5 days.

Days 1-3 as indicated on chart

Start each day at the initial rate of 1 mL/hour and if tolerated; increase by 1 mL/hour increments every 30 minutes up to the maximum tolerated infusion rate or until the weight based maximum infusion rate has been achieved. Stop infusion after 6 hours.

Day 4 onwards

Start the infusion at the maximum tolerated dose (as identified from previous 3 days).

- If tolerated the infusion rate should be increased by 1 mL/hr increments every 30 minutes up until the **weight based maximum infusion rate** has been achieved.
- If the patient experiences any unacceptable side effects, reduce the infusion rate by 1 mL/hour. This new infusion rate is the **maximum tolerated infusion rate**.
- The infusion rate should then be maintained at the maximum tolerated infusion rate or weight based maximum infusion rate.

Calculation of Flow Rate for Iloprost Infusion

Dose of Iloprost (ng/kg/ min)	Weight of patient (kg) Flow rates mls/hour										
	40	45	50	55	60	65	70	75	80	85	90
0.5	0.6	0.7	0.8	0.8	0.9	1.0	1.1	1.1	1.2	1.3	1.3
1.0	1.2	1.3	1.5	1.6	1.8	2.0	2.1	2.2	2.4	2.5	2.7
1.5	1.8	2.0	2.2	2.5	2.7	2.9	3.2	3.4	3.6	3.8	4.0
2.0	2.4	2.7	3.0	3.3	3.6	3.9	4.2	4.5	4.8	5.1	5.4

- Prior to commencement of treatment, record blood pressure, pulse, temperature and weight

• Dose Increase:

The dose should be increased as per flow rate chart every 30 minutes to a maximum of 2ng/kg/min

Side Effects

Common side effects include headache, nausea, vomiting and facial flushing. These can be treated by reducing the infusion rate and administering analgesia or anti-emetics as appropriate.

3. Education and Training

None

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Patient safety incidences and staff/patient feedback	Audit	Dr Shaffu	2 yearly	Audit presentation in meeting

5. Supporting References (maximum of 3)

References

1. Pope J, Fenlon D, Thompson A, et al. Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. Cochrane Database Syst Rev 2000; :CD000953.
2. Wigley FM, Wise RA, Seibold JR, et al. Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. A multicenter, placebo-controlled, double-blind study. Ann Intern Med 1994; 120:199.
3. Rademaker M, Cooke ED, Almond NE, et al. Comparison of intravenous infusions of iloprost and oral nifedipine in treatment of Raynaud's phenomenon in patients with systemic sclerosis: a double blind randomised study. BMJ 1989; 298:561.
4. Bettoni L, Geri A, Airò P, et al. Systemic sclerosis therapy with iloprost: a prospective observational study of 30 patients treated for a median of 3 years. Clin Rheumatol 2002; 21:244.

6. Key Words

Raynaud's phenomenon (RP); Digital ulceration

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