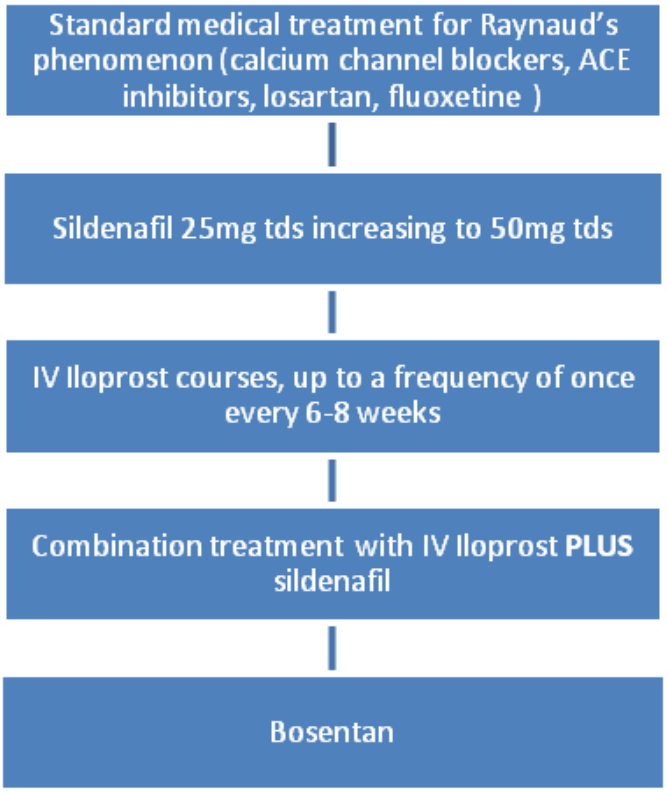
Iloprost and Bosentan - Full Clinical Guideline

Ref no:CG-RHEUM/2296/23

Sildenafil, Iloprost and Bosentan – Prescribing and monitoring in patients with digital ulceration associated with Connective Tissue Disease in Rheumatology

Sildenafil, **Ilprost** and **Bosentan** are commissioned by NHS England (NHSE)[1] and recognised 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 severe Raynaud's, secondary to Connective Tissue Disease, thathas failed to respond to standard therapies. This is in line with the following pathway:



Notes:

- Patients will have at least 6 weeks of standard medical treatment and 6 weeks of sildenafil before moving on to IV prostanoid (e.g. Iloprost). However, in cases of worsening active digital ulcer, 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.
- Nifedipine suggested first line CCB. Losartan suggested first line ARB.
- Sildenafil may be used first line if there are supply/clinical issues around prescription of first line drugs, or at clinical discretion.

Iloprost

Initiation criteria

- Indicated in on-going symptomatic Raynaud's due to Systemic Sclerosis despite at least 6 weeks of optimised first line (standard medical treatment) and 6 weeks of sildenafil.
- Also indicated in active digital ulceration where digit is at risk of critical ischemia.

Prescribing

- To be prescribed using the iloprost prescription chart (see Appendix 1) and Lorenzo.
- Baseline blood tests (full blood count, renal and liver function) should be no more than four weeks old at date of administration

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 has a change in underlying condition that means Iloprost therapy is no longer appropriate.

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 ranges from 0.5-2 nanogram/kg/min given over maximum of 6 hours.
- Dosing commences at 0.5nanogram/kg/min then increases by 0.5 nanogram/kg/min increments every 30 minutesto maximum 2 nanogram/kg/min if tolerated (see Appendix 1).
- If a reduction in dosage is required, this should be by the same increments of 0.5 nanogram/kg/ min.
- Patients should have a care plan for the treatment course to be followed by the nursing staff administering.
- Dosing rates should be documented on drug infusion chart.

Supply

In-patient: supplies via RDH pharmacy.

Administration

To be administered in accordance with 'Iloprost: Procedure for the intravenous administration in adults' drug monograph on Insite/Koha (shared with Surgery). To be administered using an electronicinfusion 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. 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.

Concomitant vasodilators

Oral vasodilators are generally discontinued for duration of infusion course.

Cautions

- Risk factors for haemorrhage
- Recent stroke (last 3 months)
- Cardiovascular disease: including recent MI (last 6 months), angina, CHD, valvular problems or heart failure
- Pregnant, breastfeeding, on hormonal contraceptives or planning to conceive.

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 sympotms
- Hyperglycaemia
- Drowsiness
- Chest pain
- syncope

Bosentan

Patients eligible with the following Indications:

Patients with Systemic Sclerosis/ Connective Tissue Disease and active digital ulcer who have either:

- Severe refractory disease: persistent or progressive ulceration of one or more digits causing or threatening tissue loss despite optimal treatment with vasodilators including IV prostanoids and oral sildenafil, or
- Multiple digital ulcers: 3 or more digital ulcers either currently or occurring in the last 12 months despite IV prostanoids and sildenafil.

Contraindications

- Acute porphyria
- Moderate or severe hepatic impairment
- Contraindicated medication (e.g. calcineurin antagonist)

Exclusions

- Patients with pulmonary arterial hypertension (PAH) and digital ulcers in whom bosentan is indicated for the treatment of their PAH; in these cases, bosentan will be prescribed by the approved PAH centres.

Prescribing

- Decision to be made by Consultant Rheumatologist in accordance with NHS clinical commissioning guidance (NHS England A13/P/e).
- Blueteq to be completed and approval number to be written on prescription (Out-patient / ePMA or drug chart).
- Prescriptions will only be dispensed if approval number present on initial prescription.
- Patients with pulmonary arterial hypertension (PAH) and DUs in whom bosentan is indicated for the treatment of their PAH; bosentan will be prescribed by the approved PAH centres

Dosing

- Bosentan treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily.
- The same recommendations apply to re-introduction of bosentan after treatment interruption.
- No adjustment needed in renal impairment.
- **Ongoing prescription :** 2 monthly for 6 months then 3 monthly. UHDB Outpatient Pharmacy

Stopping criteria

- Treatment with bosentan will be continued for a minimum of 6 months.
- Patients will be reassessed every 6 months to see if there is sufficient evidence of a response to justify continuation of treatment, the main criteria for continuation of treatment being (i) reduction in the number of new digital ulcers and (ii) documented improvement on a relevant patient reported outcome, preferably the Scleroderma Health Assessment Questionnaire (HAQ).
- Discontinuation of treatment should be considered when there is no longer any evidence of active ulceration, but in view of the preventative benefit, significant worsening of ulcers may require re-institution of treatment.

Concomitant vasodilators

- Withhold other vasodilator treatment (unless indicated for other reasons e.g. hypertension or Pulmonary arterial hypertension) until patient established on maximal therapy (8 weeks). If further acute ulceration occurs consider iloprost infusion.

Contra-indication and cautions

Contra-indicated if:

- □ Moderate to severe hepatic impairment, i.e., Child-Pugh class B or C Baseline values of liver aminotransferases, i.e., aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT), greater than 3 times the upper limit of normal
- □ Concomitant use of cyclosporine A
- □ Pregnancy (teratogenic in animal studies)
- □ Women of child-bearing potential who are not using reliable methods of contraception*

Cautioned if:

- Concomitant use with glibenclamide, fluconazole and rifampicin is not recommended.
- Concomitant administration of both a CYP3A4 inhibitor and a CYP2C9 inhibitor with Bosentan should be avoided

*Women of child-bearing potential

Women with possible pulmonary artery hypertension should only get pregnant under the preconception guidance of the medical and obstetric team as it is a relative contra-indication.

Bosentan may render hormonal contraceptives ineffective. Therefore, if used, hormonal contraceptives cannot be the sole method of contraception

Monthly pregnancy tests are recommended during treatment to allow early detection of pregnancy

Full list of Cautions, contra-indications, pregnancy & breast feeding and side effects Available from SpC:

https://www.medicines.org.uk/emc/product/821/smpc#gref

Monitoring

- LFTs to be checked at week 0, 2, 6 then monthly. In addition, liver aminotransferase levels must be measured 2 weeks after any dose increase.
- Haemoglobin to be checked monthly for 4 months then 3 monthly.

Recommendations in case of ALT/AST elevations	
ALT/AST levels	**Treatment and monitoring recommendations**
> 3 and ≤ 5 × ULN	Repeat LFTs. Review whether to continue, reduce dose or withhold bosentan. If treatment continues LTFs to be checked at least every 2weeks.
> 5 and ≤ 8 × ULN	- Repeat LFTs. Withhold bosentan. - Recheck LFT 2 weekly to ensure recovery. When returned to baselineconsider re-introduction as below.
> 8 × ULN	Treatment must be stopped and re-introduction of bosentan is not to beconsidered.

In the case of associated clinical symptoms of liver injury, i.e., nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu-like syndrome (arthralgia, myalgia, fever), **treatment must be stopped and re-introduction of bosentan is not to be considered.**

Re-introduction of treatment following LFT derangement

Re-introduction of treatment with Bosentan should only be considered if the potential benefitsof treatment with bosentan outweigh the potential risks and when liver aminotransferase levels are within pre-treatment values. The advice of a hepatologist is recommended. Re- introduction must follow the guidelines detailed in section 4.2. **Aminotransferase levels must then be checked within 3 days after re-introduction, then again after a further 2 weeks, and thereafter according to the recommendations above.**

It is recommended that haemoglobin concentrations be checked prior to initiation of treatment, every month during the first 4 months, and quarterly thereafter. If a clinically relevant decrease in haemoglobin concentration occurs, further evaluation and investigationshould be undertaken to determine the cause and need for specific treatment.

Documentation Controls

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Consultation with:	
Approved By:	Rheumatology - Dec 2023 Medicine Division – Dec 2026
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References

1. Clinical commissioning policy: sildenafil and bosentan for the treatment of digital ulceration in systemic sclerosis. July 2015. NHS England A13/P/b.
2. Denton C, Hughes M et al. BSR and BHPR guideline for the treatment of systemic sclerosis. Rheumatology 2016; 55: 1906-10.
3. Kowal-Bielecka 0, Landewe R et al. EULAR recommendations for the treatment of Systemic Sclerosis: A report from the EULAR Scleroderma Trials and Research Group (EUSTAR). Ann Rheum Dis 2009; 68(5): 620-8.

Appendix one

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 1mL/hour
- Follow the guidance below for infusion rates for specific patient groups
- Check the patient's pulse and blood pressure 30 minutes after staring the infusion and then every 30 minutes after any increase in the infusion rate.
- If tolerated the infusion rate should be increased by 1mL/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 1mL/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.

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 1mL/hour and if tolerated; increase by 1mL/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).

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.