

Clinical Commissioning Policy: Sildenafil and Bosentan for the Treatment of Digital Ulceration in Systemic Sclerosis in adults

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**Prepared by NHS England Specialised Services Clinical Reference Group for
Specialised Rheumatology**

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1 Policy Statement

NHS England will commission sildenafil and bosentan for patients requiring treatment of digital ulceration in systemic sclerosis in adults, in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to suspend or rescind policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

2 Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and

- given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About digital ulceration in systemic sclerosis

Digital ulceration (DU) (breakdown of the skin in the fingers and/or toes), from poor blood flow, affects around 1 in 3 people with systemic sclerosis (SSc). Systemic sclerosis is also known as scleroderma. So, despite the relative rarity of SSc, SSc-related digital ulcers (SSc-DUs) are frequently seen in patients with SSc living throughout England. DUs are painful, impair hand/foot function and result in significant physical and psychological impact. Patients usually require medication to improve blood flow, antibiotics, pain control and/or surgery. Deep infection of the bones (osteomyelitis) and/or gangrene can result, and amputation may be necessary.

About current treatments

Medical therapies can improve circulation and promote DU healing. Sildenafil is a potent oral treatment that improves blood flow to the digits and is available in a 'generic' form. Bosentan has been shown to reduce formation of new DU in at-risk patients by 30-50%: this is associated with improved hand function. Bosentan is licensed as a treatment for SSc-DUs, but, although advocated by European and UK guidelines, use was previously limited by cost. However, bosentan is now available in a less expensive, 'generic' form. Some patients may attend a day case unit or require hospital admission for a course of IV prostaglandin treatment in the form of iloprost or epoprostenol.

About the new treatment

The aim of this policy document is to provide a robust process that allows equitable access to treatment with sildenafil and bosentan for adult patients with SSc who have active DU which are either resistant to other treatments or recurrent.

What we have decided

NHS England has carefully reviewed the evidence to treat patients with SSc who have active DU with sildenafil and bosentan. We have concluded that there is enough evidence to make the treatment available.

3 Introduction

The products sildenafil and bosentan are recommended to be available as treatment options through routine commissioning for the treatment of adult patients with SSC who have active DU within the criteria set out within this document.

This document also describes the criteria for commissioning, governance arrangements and funding mechanisms.

The policy is restricted to adults as there is insufficient evidence to confirm safety in those age groups not included in the policy.

SSc is an uncommon systemic autoimmune disease that is capable of causing a wide range of tissue damage mediated mainly via microvascular injury and excessive fibrotic response. The most common vascular manifestation of SSc is Raynaud's phenomenon due to excessive vasoconstriction. However, more marked vascular involvement, resulting in digital ulceration, occurs at some point in up to 55% of SSc patients (Ferri et al. 2002; Khimdas et al. 2011). DUs are observed in both the limited cutaneous and diffuse cutaneous subsets of the disease and cause significant morbidity and impairment of function. Severe ulceration can lead to complications such as infection (including osteomyelitis), gangrene and amputation which can result in lengthy spells of hospital treatment and have devastating effects on hand function and the independence of the individual (Hachulla et al. 2007).

SSc patients with severe Raynaud's are managed initially with standard medical treatment such as calcium channel blockers, ACE inhibitors, losartan and/or fluoxetine. Although the cost of routine standard medical therapy is not high these initial treatments frequently lack efficacy and often result in unacceptable side effects.

When standard medical treatment is ineffective and DUs develop or progress, IV prostanoids (iloprost or epoprostenol) are used. Despite also being unlicensed for use in this indication, evidence supports the use of IV prostanoids for SSc-DU (Wigley et al. 1992; Wigley et al. 1994; Pope et al. 1998). IV prostanoids frequently succeed where initial treatment fails and are also relatively inexpensive but they

require administration on a day case basis, usually on 3-5 consecutive days, and this adds considerably to the overall cost of treatment.

The intervention involves treating adult patients with SSc who have active DU with oral agents, sildenafil and bosentan, before IV prostanoid as recommended by British Society for Rheumatology and British Health Professionals in Rheumatology guidelines (Denton et al. 2016). Active DU includes the recurrent and chronic subgroups of patients as defined from the Digital Ulcers Outcome Registry (Matucci-Cerinic et al. 2015).

Sildenafil, a phosphodiesterase type 5 inhibitor (PDE5i), is also a potent vasodilator which can be used instead of, or in combination with IV prostanoids. The cost of sildenafil has reduced significantly due to the availability of generic forms of the drug and, as an oral medication, is both more convenient for the patient and avoids day case costs.

Bosentan, an endothelin receptor antagonist, is licensed for use in DUs and has been proven to reduce the incidence of new DU formation in patients with active DU (Korn et al. 2004; Matucci-Cerinic et al. 2011). A generic form of bosentan has recently become available, significantly reducing the cost.

4 Definitions

Systemic sclerosis (SSc): a systemic, autoimmune-mediated connective tissue disease that is diagnosed according to either the 1980 ACR or the more sensitive 2013 ACR-EULAR classification criteria.

Raynaud's phenomenon: a condition resulting in discolouration of the fingers and/or toes due to decreased blood supply.

Sildenafil: a phosphodiesterase type 5 inhibitor (PDE5i) which is a potent vasodilator. It is not currently licensed for treatment of Raynaud's phenomenon or DUs in SSc patients. Generic forms of sildenafil (e.g. 25mg and 20mg tablets) are available.

Bosentan: an oral endothelin receptor antagonist (ERA) which blocks both ET_A and ET_B receptors and is licensed for the prevention of formation of new DU in patients with SSc.

5 Aims and Objectives

This policy considers: the use of sildenafil and bosentan for the treatment of adult patients with SSc who have active DU

The objectives were to:

- Establish the clinical effectiveness, safety and cost-effectiveness of sildenafil and bosentan for the treatment of adult patients with SSc who have active DU
- To reposition bosentan in the management pathway for adult patients with SSc who have active DU in view of the significant reduction in cost due to the availability of a generic form of the drug
- Identify the clinical criteria to be used to select suitable patients to be considered for the use of sildenafil and bosentan
- Define commissioning arrangements required for the use of sildenafil and bosentan

6 Epidemiology and Needs Assessment

The number of patients with SSc and DUs of sufficient severity to require treatment with bosentan has not been precisely determined. The age of onset of SSc is often between 20 and 50 years of age, however, SSc can present in people older than this and in children. Earlier-onset SSc has been associated with a higher prevalence of DUs (Alba et al. 2014). Estimates for the prevalence of SSc vary from 88 to 200 cases per million population (Allcock et al. 2004; Mayes, 2003). Assuming the true value in the UK is in the region of 100 cases per million population, there are approximately 8,000 patients with SSc in England. In one UK cohort of 1168 patients with SSc followed for 18 months (Nihtyanova et al. 2008), 17.4% were identified as having severe digital vasculopathy leading to complications including ulceration, critical ischaemia and gangrene, resulting in hospital admissions for IV prostanoids, antibiotics and sometimes surgical intervention. Taking these

prevalence estimates into account (England population ~55M, 100 cases per million, 17% prevalence DU), in England the number of patients who might be eligible for treatment under this policy is approximately 1000 per year. It is estimated that 10% of patients with this severity of disease might satisfy the criteria for treatment with bosentan described below in any one year. With bosentan positioned after sildenafil and before IV prostanoid in the treatment pathway, it is expected that there will be at least a 10% reduction in the use of IV prostanoid and subsequent increase in the use of bosentan. Therefore, the number of patients in England likely to require initiation or ongoing treatment with bosentan is over 100 per annum.

7 Evidence Base

NHS England has concluded that there is sufficient evidence to support the routine commissioning of sildenafil and bosentan for the treatment of adult patients with SSc who have active DU.

Sildenafil has been shown in open label, pilot studies (Brueckner et al. 2010; Kumar et al. 2013) and one small placebo-controlled crossover study (Fries et al. 2005) to have positive effects on DU healing and reduction in severity of Raynaud's phenomenon in SSc patients.

Two randomised, placebo-controlled double-blind studies have examined the role of bosentan in the reduction of DU formation in SSc patients. RAPIDS-1 studied 122 SSc patients treated for 16 weeks with either bosentan or placebo and showed a 48% reduction in the formation of new ulcers during this period (Korn et al. 2004). Patients with DU at the start of the trial were more at risk of developing ulcers, but a 50% reduction in new ulcer formation was also demonstrated in this subgroup. A significant improvement in hand function was demonstrated in the bosentan-treated patients. In the subsequent RAPIDS-2 study (Matucci-Cerinic et al. 2011), all SSc patients (n=188) had active DU at commencement of the trial and were followed for 24 weeks. Bosentan treatment was associated with a 30% reduction in new ulcer formation compared with placebo although no effect on DU healing was found. Post hoc analysis suggested that patients with more severe DU disease obtained the most benefit as cases with a very high number of new ulcers were only seen in the placebo treated cases and there was more benefit in

patients with 3 or 4 ulcers at study onset. Also, in RAPIDS-1, those who had an active ulcer at start of the study benefitted more than those with just a history of previous DU. The results of the above randomised, placebo-controlled studies are borne out in observational studies for up to 3 years (Tsifetaki et al. 2009; Fanauchi et al. 2009).

A meta-analysis of RCTs assessing efficacy of various therapies in healing and preventing DUs in SSc found:

- PDE5 inhibitors resulted in significant DU healing (RR 3.28, [95% confidence interval (95% CI) 1.32, 8.13], P = 0.01),
- bosentan significantly reduced mean number of new DUs (standardised mean difference (SMD) -0.34, [95% CI -0.57, -0.11], P = 0.004) and
- IV iloprost significantly prevented new DU formation (SMD -0.77, [95% CI -1.46, -0.08], P = 0.03) (Tingey et al. 2013).

At present, the evidence base for the **cost**-effectiveness of bosentan treatment to prevent formation of DU in SSc patients is limited. The cost of treatment is relatively high. However, cohort studies show that patients with multiple ulcers or severe ulceration with ischaemic complications are likely to require lengthy or repeated hospital stays, frequent antibiotic treatment, digital sympathectomy or surgery and are therefore likely to have high consumption of healthcare resources. In addition, increasing numbers of DUs are associated with decreased work capacity and increased reliance on others for activities of daily living (Berezne et al. 2011). Treatment to reduce the burden of DUs in this patient group could therefore reasonably be expected to be associated with a reduction in these healthcare and societal costs. Recent published data from the large (over 4000 patient) DUO digital ulcer registry confirm that reduction in DU number is directly linked to reduced paid and unpaid support, reduced time missed from employment and reduced major medical complications that require hospital-based treatments (Guillevin et al. 2013).

8 Criteria for Commissioning

The EULAR / EUSTAR recommendations (Kowel-Bielecka et al. 2009) and the UK Scleroderma Study Group (UKSSG) pathway, state standard pharmacological treatment of severe Raynaud's phenomenon and DU should include use of calcium channel blockers. It is expected that patients treated under this guideline will already have received such treatment (Denton et al. 2016). The revised policy states that sildenafil remains the next treatment option, but sildenafil is then followed by bosentan and reserves IV prostanoids for patients with severe acute disease or if they are unable to tolerate sildenafil and bosentan. Bosentan should now be used prior to IV prostanoids due to the reduced cost and increased convenience for patients. The following UKSSG pathway, which will be readily available to all specialist centres and accessible to all via the UKSSG web-link (<http://www.scleroderma-royalfree.org.uk/>), is recommended, with patient consent at all levels, and takes into consideration the importance of both DU healing and subsequent prevention:

Sildenafil should be prescribed for adult patients, noting the contraindications and special precautions. The dose will be titrated according to response and tolerability. The dose may range from 25mg daily to 50mg four times per day.

Bosentan:

The recommended dose for bosentan is 125mg twice daily.

Adult patients eligible with the following indications:

Patients with SSc and active DUs despite full dose sildenafil, 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 oral sildenafil, or
- Multiple DUs: 3 or more DUs either currently or occurring in the last 12 months despite sildenafil.

Contraindications:

- Acute porphyria
- Moderate or severe hepatic impairment

- Contraindicated medication (e.g. calcineurin antagonist)
- Concomitant use of cyclosporine A
- Pregnancy (drug is teratogenic)
- Women of childbearing potential who are not using reliable methods of contraception
- Baseline liver aminotransferase levels greater than 3 times the upper limit of normal

Exclusions:

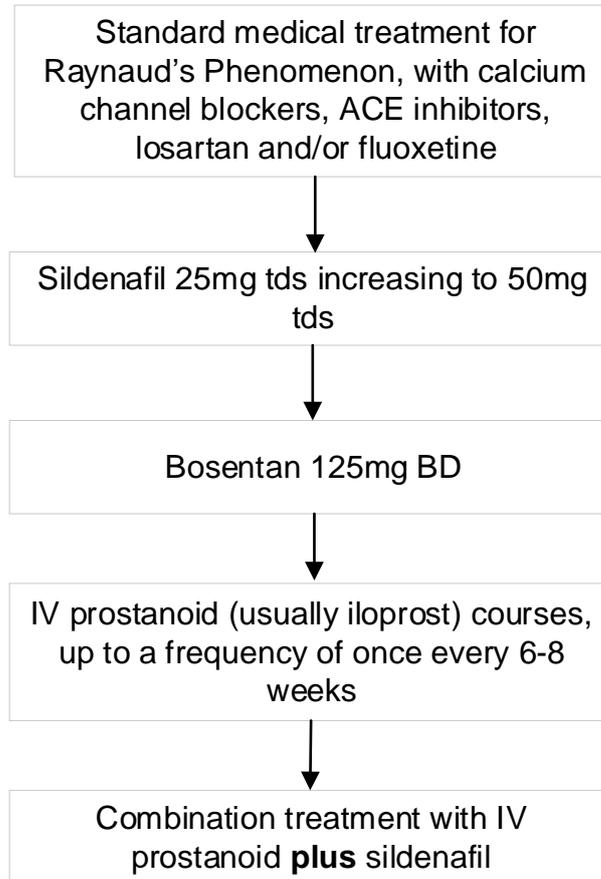
- Patients with pulmonary arterial hypertension (PAH) and DUs in whom bosentan is indicated for the treatment of their PAH; in these cases, bosentan will be prescribed by the approved PAH centres.

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.

9 Patient Pathway

The pathway is outlined below:



Patients will usually have at least 6 weeks of standard medical treatment and 6 weeks of sildenafil before moving on to bosentan. However, in cases of worsening active DU, the initiation of bosentan should be considered sooner as patients may require escalation to IV prostanoid earlier in order to save the digit.

Patients should be managed in accordance with the existing pathways (including non-pharmacological interventions). The oral agents (sildenafil and bosentan) should be prescribed before IV prostanoid (Denton et al. 2016). The use of bosentan is expected to reduce the need for IV prostanoid. Patients requiring treatment with bosentan will be referred by their usual consultant rheumatologist for an opinion from a specialised rheumatology centre. This can include discussion at the regional specialised rheumatology MDT meeting.

PAH Pathway:

Patients with pulmonary arterial hypertension (PAH) and DUs in whom bosentan is indicated for the treatment of their PAH; in these cases bosentan may be prescribed with follow up of the patient's DUs by a Rheumatology service.

10 Governance Arrangements

NHS England (2013). *2013/14 NHS Standard Contract for Specialised Rheumatology Services (Adult)*. NHS England. Accessed 23 May 2019: <<https://www.england.nhs.uk/wp-content/uploads/2013/06/a13-spec-rheumatology.pdf>>.

Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process. Blood drug safety monitoring of bosentan should be performed as per the product license.

Provider organisations must register all patients using software such as the prior approval system and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

All patients will be assessed by a multidisciplinary specialised rheumatology team and will be subject to standard metrics as per section below.

11 Mechanism for Funding

Contractual arrangements are managed through the responsible sub-regional commissioning team.

This policy has been agreed on the basis of NHS England's understanding of the funding responsibility, as at the time of the policy's adoption. Should these prices materially change, and in particular should they increase, NHS England may need to review whether the policy remains affordable and may need to make revisions to the published policy.

Standard medical treatment and sildenafil will not be charged to NHSE as payment by results (PbR) excluded drugs.

12 Audit Requirements

Not Applicable

13 Documents That Have Informed This Policy

This document updates and replaces Clinical Commissioning Policy: A13/P/b Sildenafil and Bosentan for the Treatment of Digital Ulceration in Systemic Sclerosis:
NHS England (2015). *Clinical Commissioning Policy: Sildenafil and Bosentan for the Treatment of Digital Ulceration in Systemic Sclerosis*. NHS England. Accessed 26 April 2019: <<https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/a13pb-sildenafil-bosentan-oct15.pdf>>.

14 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

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