Clinical Commissioning Policy: Sildenafil and bosentan for the treatment of digital ulceration in systemic sclerosis

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NHS England Clinical Commissioning Policy: Sildenafil and bosentan for the treatment of digital ulceration in systemic sclerosis

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Contents

Policy Statement
NHS England will commission sildenafil and bosentan for the treatment of digital ulceration in systemic sclerosis 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.

Equality Statement
Throughout the production of this document, due regard has been given 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 in under the Equality Act 2010) and those who do not share it.

Plain Language Summary
Digital ulceration (breakdown of the skin in the finger and/or toes), from poor blood flow, affects around 1 in 3 people with systemic sclerosis (SSc). So, despite the relative rarity of SSc, SSc-related digital ulcers (DUs) are regularly seen throughout England. DUs are painful, impair hand/foot function and result in significant physical and psychological impact. Patients frequently 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.

Medical therapies can improve circulation and promote DU healing. Therapies currently available for use within the NHS either have limited efficacy/side effect profile or require hospital administration for intravenous therapy. Sildenafil is a potent oral treatment infrequently used in the UK for SSc as it is unlicensed and was expensive. However, sildenafil is now available in a less expensive, ‘generic’ form. Although all these treatments can improve DU healing, they have not been shown to reduce occurrence of new DU. 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 has been limited by cost.

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

1. Introduction

Systemic sclerosis (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, but more marked vascular involvement resulting in digital ulceration occurs at some point in up to 55% of SSc patients (1,2). Digital ulcers (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 (3).

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 only short-acting nifedipine is licensed for Raynaud's management. 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 DU develops, intravenous (IV) prostanoids (iloprost or epoprostenol) are used (see pathway in '7. Criteria for commissioning'). Despite also being unlicensed for use in this indication, evidence supports the use of IV prostanoids for SSc-DU (4-10). IV prostanoids frequently succeed where initial treatment fails and are also relatively inexpensive but they require administration on a day case basis, usually on 5 consecutive days, and this adds considerably to the overall cost of treatment.

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 recently 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, has been proven and is licensed to reduce the incidence of new DU formation in patients with active DU (11,12).

2. Definitions

Systemic sclerosis (SSc) is 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.

Sildenafil is a phosphodiesterase type 5 inhibitor (PDE5i) which is a potent vasodilator. It is licensed (as Viagra) for the treatment of erectile dysfunction and (as Revatio) for the treatment of pulmonary arterial hypertension (PAH), but is not currently licensed for treatment of Raynaud's phenomenon or digital ulcers (DUs) in SSc patients. A generic form of sildenafil (25mg tablets) recently received its license.

Bosentan is 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 and for PAH.

3. Aim and objectives

This policy aims to ensure equitable and clinically appropriate access to treatment with sildenafil and bosentan for patients with SSc who have active DU, taking into account the cost of therapy, likely benefits and alternative available treatment approaches for DUs in SSc.

4. 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. To date, patients in England treated with bosentan for this indication have received access via Individual Funding Requests (IFRs), but, since no consistent criteria have been used to determine the outcome of such requests, it is unlikely that the number of patients treated currently is an accurate reflection of demand. Estimates for the prevalence of SSc vary from 88 to 200 cases per million population (13, 14): if we assume that the true value in the UK is in the region of 150 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 (15), 17.4% were identified as having severe digital vasculopathy leading to complications including ulceration, critical ischaemia and gangrene, resulting in hospital admissions for intravenous prostanoids, antibiotics and sometimes surgical intervention. Estimating that 10% of patients with this severity of disease might satisfy the criteria for treatment with bosentan described below in any one year, the number of patients in England likely to require initiation or ongoing treatment per annum is 140.

5. Evidence base

Sildenafil has been shown in open label, pilot studies (16,17) and one small placebo-controlled crossover study (18) 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 (11). 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 (12), 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 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 (19, 20).

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) (21).

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 (see below). 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 (22). 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 (23).

6. Rationale behind the policy statement

This policy has two main aims: firstly, to reposition sildenafil in the management pathway for DU in SSc in view of the significant reduction in cost due to the availability of a generic form of the drug; secondly, to provide access to bosentan for SSc patients with severe, refractory or multiple DUs provided that the patients have received an adequate trial of other therapies. The use of sildenafil will be a cost-effective option compared with regular courses of iloprost. The latter may be given once every 2 to 3 months in patients with severe disease.

There are no head to head studies comparing the efficacy of these drugs. Bosentan is the only therapy licensed for the prevention of formation of new DU in patients with SSc. The cost of treatment is in the region of £20,000 per patient per annum, but the available data suggest that this drug is likely to be cost-effective in patients with severe disease due to the morbidity and healthcare costs of managing refractory DUs.

7. Criteria for commissioning

As per EULAR / EUSTAR recommendations (24) and the UK Scleroderma Study Group (UKSSG) pathway, standard pharmacological treatment of severe Raynaud's phenomenon and DU should include use of calcium channel blockers and IV prostanoids. It is expected that patients treated under this guideline will already have received such treatment. In view of the reduced cost and efficacy of sildenafil, this should be routinely used in SSc patients with active DU prior to treatment with bosentan. 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 proposed, with patient consent at all levels, and takes into consideration the importance of both DU healing and subsequent prevention:

Sildenafil should be prescribed, noting the contraindications and special precautions.

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

Bosentan:

Indications:
Patients with SSc and active DUs 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 DUs: 3 or more DUs either currently or occurring in the last 12 months despite IV prostanoids and sildenafil.

Contraindications:

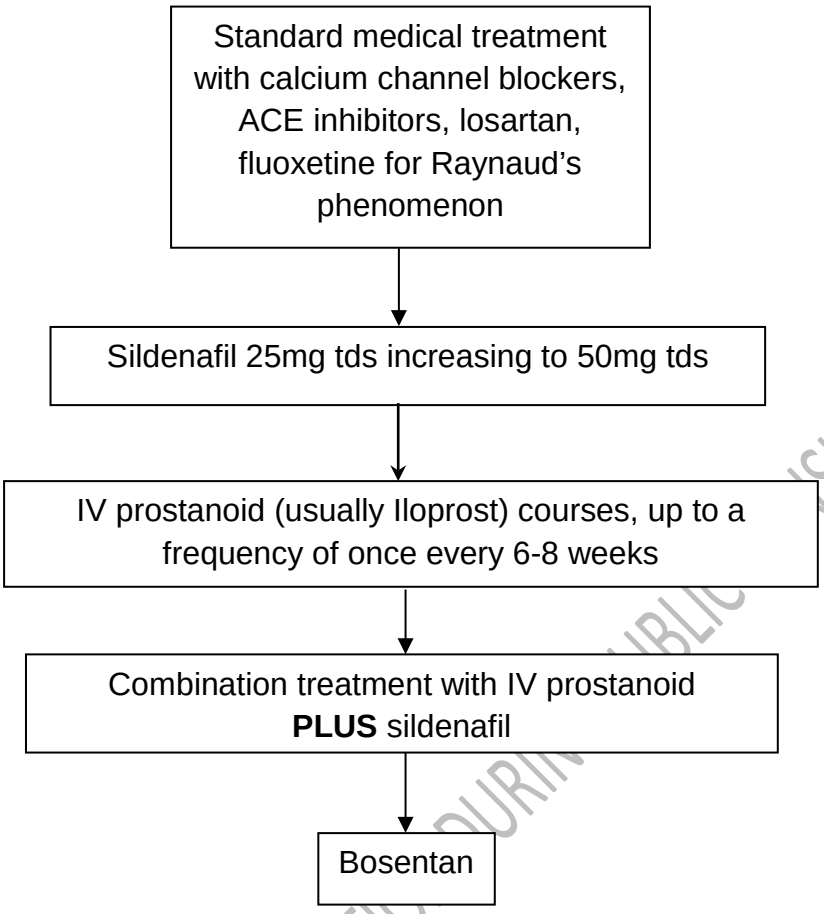
- Acute porphyria
- Moderate or severe hepatic impairment
- Contraindicated medication (e.g. calcineurin antagonist)

Exclusions:

- Patients with pulmonary arterial hypertension (PAH) and 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.

The pathway is outlined below*:



*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.

8. Patient pathway

Patients should be managed in accordance with the existing pathways (including non-pharmacological interventions) referred to in section 7. It is proposed that sildenafil should be routinely prescribed first line as an alternative to treatment with IV prostanoid, or prescribed in combination with IV prostanoid according to the treatment pathway detailed in section 7. Patients requiring treatment with bosentan will be referred by their usual consultant rheumatologist for an opinion from a specialised rheumatology centre. If, after assessment by the specialised centre team, the agreed commissioning criteria are met (to be recorded on an agreed proforma), bosentan can be prescribed by the specialised centre.

9. Governance arrangements

All patients will be assessed by a multidisciplinary specialised rheumatology team and will be subject to standard metrics as per section 11 below.

10. Mechanism for funding

Through the responsible Area Team.

11. Audit requirements

All patients treated with bosentan under the terms of this policy must be entered onto the existing registry for SSc patients with DU, the DUO registry (23). This was set up as part of the EMA license for use of bosentan for prevention of DU and collects multiple data fields including DU history and status and functional information including work status. The Scleroderma HAQ will also be routinely performed, to inform impact of management on lifestyle. Data on side effects of therapy will be collected.

12. Documents which have informed this policy

Bosentan treatment for prevention of DUs in SSc has not been evaluated by NICE. A list of references is given below.

13. Links to other policies

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

14. Date of review

July 2016

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Version Control Sheet

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