NICE advice

Digital ulcers: sildenafil

Evidence summary
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Key points from the evidence

The content of this evidence summary was up-to-date in March 2015. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

Data on the efficacy of sildenafil for managing digital ulcers associated with systemic sclerosis are limited. Individual randomised controlled trials (RCTs) have not shown a statistically significant treatment effect of sildenafil on digital ulcers. However, a small observational study has shown some benefit for sildenafil on ulcer healing and a meta-analysis has shown benefit for phosphodiesterase type 5 (PDE5) inhibitors as a drug class for ulcer healing and improvement. Larger RCTs, particularly with other comparative treatments, are needed to clarify efficacy and safety of using sildenafil for managing digital ulcers.

Regulatory status: off-label. This topic was prioritised because there was a high volume of requests from the NHS. PDE5 inhibitors, such as sildenafil, are used in the management of digital ulcers, but none is specifically licensed for this indication. NHS England has published a draft clinical commissioning policy on sildenafil and bosentan for the treatment of digital ulceration in systemic sclerosis which is currently undergoing a 3-month public consultation (consultation ends 30 April 2015).

The Department of Health has amended regulations to allow unrestricted prescribing of generic sildenafil for men with erectile dysfunction.

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Effectiveness	Safety
• 2 small, 4-week, double-blind RCTs in people with Raynaud's phenomenon generally secondary to systemic sclerosis (n=20 and 57, which were reported in a meta-analysis) found no statistically significant benefit for sildenafil compared with placebo for digital ulcer healing or improvement, but the trials were underpowered for these end points. • A small, 6-month prospective uncontrolled study in people with systemic sclerosis (n=19) found a statistically significant benefit with sildenafil for the primary outcome of ulcer healing (p<0.001). • A meta-analysis of 3 small RCTs found a statistically significant benefit for PDE5 inhibitors as a class compared with placebo for digital ulcer healing (p=0.01) and improvement (p=0.002).	• Commonly reported adverse events with sildenafil in the 2 RCTs and 1 observational study were headache, dyspepsia, facial flushing, palpitations, arthralgia and myalgia. • The summaries of product characteristics for licensed sildenafil products provide information on contraindications, cautions and interactions. Serious adverse cardiovascular events have been reported and cautions include use in people with hypotension, fluid depletion, severe left ventricular outflow obstruction or autonomic dysfunction. Sildenafil is contraindicated in people with severe hypotension, or a recent history of stroke or myocardial infarction.

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Patient factors	Resource implications
• About 10% of people discontinued treatment in the 2 RCTs and 1 observational study because of treatment-related adverse events. • Sildenafil is an oral treatment taken on a daily basis.	• The estimated 28-day cost of sildenafil (Revatio) at a dose of 20 mg 3 times daily is £416.58 (MIMS, February 2015; excluding VAT). • The estimated 28-day cost of generic sildenafil at a dose of 25 mg to 50 mg 3 times daily is £22.89 to £23.73 (Drug Tariff February 2015; excluding VAT). • The estimated 28-day cost of bosentan at a dose of 62.5 mg to 125 mg twice daily is £1510.21 (MIMS, February 2015; excluding VAT). • The estimated drug cost for a 5-day iloprost infusion (1 treatment cycle) is approximately £425 to £475, excluding VAT and associated hospital costs.

Introduction and current guidance

Digital ulcers usually occur in people who have severe Raynaud's phenomenon secondary to systemic sclerosis (Steen et al. 2009), and are associated with fibrosis and diseased blood vessels in fingers or toes (digital vasculopathy).

Digital ulcers are difficult to treat, painful, may limit hand function, can develop into serious complications and impair overall quality of life. Treatment aims to improve symptoms, prevent and heal ulcers, and reduce associated morbidity and mortality.

The European League against Rheumatism (EULAR) Scleroderma Trials and Research group published recommendations for managing systemic sclerosis-related digital vasculopathy in 2009 (Kowal-Bielecka et al. 2009). No formal recommendation on using sildenafil was included. However, consensus best practice recommendations for digital vasculopathy developed by the UK Scleroderma Study Group advocate using PDE5 inhibitors, such as sildenafil and tadalafil, as a treatment option for ulcers that are difficult to treat. An update of the EULAR recommendations is expected in 2015.

Full text of introduction and current guidance.

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Product overview

Sildenafil is a PDE5 inhibitor with a vasodilator effect. Sildenafil is licensed in the UK for treating pulmonary hypertension in adults and children, and for treating erectile dysfunction in men. Prescribing of generic sildenafil is unrestricted for men with erectile dysfunction.

See the summaries of product characteristics of sildenafil products for more information on these indications. No sildenafil product is licensed for managing digital ulcers; therefore using sildenafil for this indication is off-label.

Full text of product overview.

Evidence review

Systemic sclerosis is a rare condition and RCTs in this area are difficult to undertake. Data on managing digital ulcers with sildenafil are therefore very limited. This evidence summary is based on the best available evidence for using sildenafil to manage digital ulcers in people with systemic sclerosis, including 2 small RCTs (Fries et al. 2005 and Herrick et al. 2011) and 1 observational study (Brueckner et al. 2010). In the original published papers of the 2 RCTs, data on ulcer healing were not reported. However, outcome data were collated and evaluated in a meta-analysis that focused on healing and preventing digital ulcers (Tingey et al. 2013). The meta-analysis considered PDE5 inhibitors as a drug class, and the pooled analysis included results from the 2 RCTs of sildenafil (Fries et al. 2005 and Herrick et al. 2011) and an RCT of tadalafil (Shenoy et al. 2010).

- Both RCTs considered the effect of sildenafil in people with Raynaud's phenomenon generally secondary to systemic sclerosis. The smaller, single-centre, German crossover study (n=20) compared sildenafil (50 mg twice daily) with placebo for 4 weeks (Fries et al. 2005) and the second larger, multicentre European RCT (n=57; Herrick et al. 2011) compared modified-release sildenafil (titrated up to 200 mg daily, equivalent to 150 mg immediate release) with placebo for 28 days. The effect of sildenafil on ulcers was a primary outcome in the crossover study but only an exploratory outcome in the second, larger RCT.
- In Fries et al. (2005), all 6 people with ulcers at baseline reported some healing during treatment with sildenafil, and ulcers completely healed in 2 people (no statistical data analysis reported).
- In Herrick et.al. (2011), the per-protocol population was 45 people (sildenafil, n=20; placebo, n=25). Five (25%) people had digital ulcers at baseline compared with 3 (15%) people after 28 days of treatment with sildenafil. In the placebo group, 3 (12%) people had digital ulcers at

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baseline compared with 5 (20%) people at day 28. No data analysis was reported for ulcer healing and data on the number of people with ulcers were only included in an abstract (Herrick et al. 2009).

- The meta-analysis (Tingey et al. 2013) reported that there was no statistically significant benefit of sildenafil compared with placebo for ulcer healing (p=0.27 and p=0.39) or ulcer improvement (p=0.06) in the individual trials. However, these trials were underpowered for these end points. The meta-analysis pooled effect for PDE5 inhibitors as a class (including trials of sildenafil and tadalafil) showed a statistically significant benefit compared with placebo for digital ulcer healing (RR 3.28, 95% confidence interval [CI] 1.32 to 8.13, p=0.01) and digital ulcer improvement (RR 4.29, 95% CI 1.73 to 10.66, p=0.002).

- Observational data from a small, single-centre pilot study (n=19; Brueckner et al. 2010), which considered maximally tolerated doses of sildenafil (up to 150 mg daily, mean daily dose 114 mg) for a mean duration of 5.2 months, found a statistically significant reduction in the number of digital ulcers from baseline (mean difference 2 ulcers per person, p<0.001). However, 9 people developed 12 new ulcers between them.

- Across both RCTs (Fries et al. 2005 and Herrick et al. 2011) more people experienced adverse events in the sildenafil groups compared with the placebo groups. The most common adverse event for people taking sildenafil was headache (20% in Fries et al. 2005 and 50% in Herrick et al. 2011). Other less frequent adverse events included dyspepsia, arthralgia and myalgia. No deaths or serious adverse events were reported. A total of 6 people across both studies stopped taking sildenafil because of treatment-related adverse effects (mainly headache and myalgia).

- In the observational study (Brueckner et al. 2010), mild adverse effects were common (47%). Adverse effects included palpitations (21%), facial flushing (21%) and peripheral oedema (16%). In 3 people with hypertension, antihypertensive treatment was reduced during sildenafil treatment. Two people stopped treatment because of adverse effects.

- The small RCTs and the observational study have a number of limitations and the results are difficult to relate to clinical practice. In particular, the literature highlights the difficulty investigators faced defining and standardising digital ulcer indicators and end points when undertaking research in this area.

Full text of evidence review.

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Context and estimated impact for the NHS

The estimated 28-day cost of generic sildenafil at a dose of 25 mg to 50 mg 3 times daily is £22.89 to £23.73 (Drug Tariff February 2015; excluding VAT). The oral sildenafil product licensed for pulmonary hypertension (Revatio) is more expensive, at an estimated 28-day cost of £416.58 for 20 mg 3 times daily (MIMS February 2015; excluding VAT). Consensus best practice recommendations for digital vasculopathy include the use of bosentan and prostanoids such as iloprost in some people. Bosentan, taken orally, is licensed for preventing digital ulcers in people with systemic sclerosis and pre-existing ulcers (it has not been shown to heal existing digital ulcers). Iloprost injection is unlicensed in the UK but can be supplied on request from the manufacturer. Iloprost is given by infusion, which involves admission to hospital as either a day case or as an inpatient.

Full text of context and estimated impact for the NHS.

Information for the public

A plain English summary is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with digital ulcers who are thinking about trying sildenafil.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance**.

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Full evidence summary

Introduction and current guidance

Digital ulcers are usually a complication of secondary Raynaud's phenomenon and are most frequently seen in the context of connective tissue diseases related to systemic sclerosis. Other causes include ischaemia due to vascular disease, repetitive microtrauma and dry skin (Steen et al. 2009).

Systemic sclerosis is a multisystem autoimmune disease in which there is increased fibroblast activity resulting in abnormal growth of fibrous connective tissue (fibrosis). This causes fibrosis of the skin, the gastrointestinal tract and other internal organs (NHS choices: scleroderma). In more than 90% of people with systemic sclerosis, skin fibrosis manifests as Raynaud's phenomenon (Steen et al. 2009), characterised by narrowing of the blood vessels (vasospasm) in response to cold, change in temperature or emotional stress (NHS choices: Raynaud's phenomenon). This response restricts blood flow to digital extremities (fingers and toes).

Digital ulcers can arise in people with severe Raynaud's secondary to systemic sclerosis, due to underlying diseased blood vessels (vasculopathy) and fibrosis. Digital ulcers are a major clinical problem when managing systemic sclerosis, occurring in about 30% of people with systemic sclerosis each year. Ulcers may develop on finger tips or joints, elbows, ankles and toes (Strange and Nash 2009). They are painful, can cause functional impairment, and impact on the person's quality of life. Complications of digital ulcers include gangrene, osteomyelitis and amputation (Steen et al. 2009).

Treatment for digital ulcers aims to reduce the associated symptoms such as pain and loss of hand function, improve circulation, prevent infection and new ulcers from developing, promote healing of established ulcers, and overall to improve the person's quality of life and reduce the need for hospital admissions (Steen et al. 2009).

Evidence-based, consensus-derived recommendations for treating systemic sclerosis were published by the European League against Rheumatism (EULAR) Scleroderma Trials and Research group in 2009 (Kowal-Bielecka et al. 2009). The approach to managing systemic sclerosis-related digital vasculopathy (Raynaud's phenomenon and digital ulcers) is to address the background Raynaud's phenomenon severity. With regard to digital vasculopathy the EULAR recommendations state:

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- 'A meta-analysis on dihydropyridine-type calcium-channel blocker and 1 meta-analysis on prostanoids indicate that nifedipine and intravenous iloprost reduce the frequency and severity of systemic sclerosis-Raynaud's phenomenon attacks. Dihydropyridine-type calcium-channel blocker, usually oral nifedipine, should be considered for first-line therapy for systemic sclerosis-Raynaud's phenomenon, and intravenous iloprost, or other available intravenous prostanoids for severe systemic sclerosis-Raynaud's phenomenon.

- 2 randomised controlled trials (RCTs) indicate that intravenous prostanoids (particularly intravenous iloprost) are efficacious in healing digital ulcers in people with systemic sclerosis. Intravenous prostanoids (in particular iloprost) should be considered in the treatment of active digital ulcers in people with systemic sclerosis.

- Bosentan has no confirmed efficacy in the treatment of active digital ulcers in people with systemic sclerosis. Bosentan has confirmed efficacy in 2 high quality RCTs to prevent digital ulcers in people with diffuse systemic sclerosis, in particular in those with multiple digital ulcers. Bosentan should be considered in diffuse systemic sclerosis with multiple digital ulcers after failure of calcium antagonists and, usually, prostanoid therapy.'

No evaluation of published evidence or formal recommendation on using sildenafil for managing digital ulcers was given. The report states that research is needed to evaluate the efficacy and safety of sildenafil when used to manage digital ulcers associated with systemic sclerosis. An update of the EULAR recommendations is expected in 2015.

Bosentan (Tracleer) is the only product licensed in the UK to prevent new digital ulcers developing in people with systemic sclerosis and ongoing digital ulcer disease. The summary of product characteristics for bosentan states that it has not been shown to heal existing digital ulcers. No licensed version of intravenous iloprost or other prostanoids is available in the UK.

The British Society for Rheumatology is developing scleroderma management guidelines, and Consensus best practice recommendations for scleroderma have been developed by the UK Scleroderma Study Group. The UK Scleroderma Study Group recommendations represent agreed practice across UK specialist centres, and complement the EULAR evidence-based treatment recommendations. The consensus recommendations include pathways for digital vasculopathy in systemic sclerosis; they advocate phosphodiesterase type 5 (PDE5) inhibitors, such as sildenafil and tadalafil, as a treatment option for people with refractory Raynaud's; in people with non-healing, recalcitrant digital ulcers; or critical digital ischaemia when first-line therapy is inadequate.

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NHS England has published a draft clinical commissioning policy on sildenafil and bosentan for the treatment of digital ulceration in systemic sclerosis which is currently undergoing a 3-month public consultation that ends 30 April 2015.

Product overview

Drug action

Sildenafil is a potent and selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Inhibition of the PDE5 enzyme increases the available intracellular cGMP, which leads to vasodilation in the systemic circulation (sildenafil summaries of product characteristics).

Regulatory status

Sildenafil is licensed in the UK for treating pulmonary arterial hypertension in adults and children. Sildenafil is also licensed for treating erectile dysfunction in men. The Department of Health has amended regulations to allow unrestricted prescribing of generic sildenafil for men with erectile dysfunction.

See summaries of product characteristics of sildenafil products for more information on these indications.

No sildenafil product is licensed for treating or preventing digital ulcers, therefore using sildenafil for this indication is off-label.

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using sildenafil outside its authorised indications.

Cost

Generic sildenafil is £1.09 for 4×25 mg tablets, £1.13 for 4×50 mg and £1.22 for 4×100 mg tablets (excluding VAT; costs taken from Drug Tariff, February 2015).

The sildenafil product that is licensed for managing pulmonary hypertension (Revatio) is £446.33 for 90×20 mg tablets, £186.75 for 112 ml×10 mg/ml oral suspension and £45.28 for 20 ml×0.8 mg/ml solution for injection (excluding VAT; costs taken from MIMS, February 2015).

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Evidence review

This evidence summary is based on the best available evidence for using sildenafil to manage digital ulcers in people with systemic sclerosis. This includes a meta-analysis of various different therapies (including PDE5 inhibitors) for healing and preventing digital ulcers in systemic sclerosis (Tingey et al. 2013). The meta-analysis includes 2 small, double-blind randomised control trials (RCTs) that specifically considered sildenafil for treating Raynaud's phenomenon generally secondary to systemic sclerosis (Fries et al. 2005 and Herrick et al. 2011). A small, prospective pilot study that looked at the effect of sildenafil on healing digital ulcers in people with systemic sclerosis (Brueckner et al. 2010) is also discussed briefly.

There have been a number of other case series, reports and small clinical studies that have described using sildenafil to treat Raynaud's phenomenon (De LaVega and Derk 2009) but these are lower grade evidence and are not included in this evidence summary. A prospective RCT that evaluated the effect of sildenafil on healing digital ulcers in people with systemic sclerosis has been completed but the results remain unreported and unpublished (Clinical trials identifier NCT01295736).

Clinical effectiveness

The authors of the meta-analysis (Tingey et al. 2013) found 31 RCTs (n=1989) that met the eligibility inclusion criteria. These studies compared various different therapies with placebo or active treatment for healing and preventing digital ulcers in people with systemic sclerosis, and had primary, secondary or exploratory outcomes that investigated digital ulcers. The meta-analysis included data from 3 small RCTs of PDE5 inhibitors. There were 2 small double-blind RCTs of sildenafil for the treatment of Raynaud's phenomenon (Fries et al. 2005 and Herrick et al. 2011) and 1 small RCT of tadalafil (Shenoy et al. 2010). Pooled data analysis reported in the meta-analysis is not considered in detail in this evidence summary because the results for PDE5 inhibitors included the tadalafil study.

Fries et al. (2005) was a fixed-dose, single-centre, German crossover study in which 20 people with secondary (n=16) or primary Raynaud's phenomenon (n=2) resistant to vasodilatory treatment were randomised to either sildenafil 50 mg twice daily or placebo for 4 weeks (2 people stopped sildenafil and withdrew because of adverse effects). After a 1-week wash-out period, people in the trial were then switched to the alternative treatment for a further 4 weeks. Six people had digital ulcers at baseline. The primary outcomes were frequency and duration of Raynaud attacks, capillary flow velocity and evolution of trophic digital lesions.

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For people who were taking sildenafil, the frequency of Raynaud attacks was statistically significantly lower (p=0.0064) and the cumulative attack duration statistically significantly shorter (p=0.0038). In all 6 people with secondary Raynaud's phenomenon who had chronic digital ulcerations, trophic lesions began to heal during treatment with sildenafil. In 2 people, ulcerations completely disappeared. The investigators stated that ulcerations reappeared or progressed again after treatment with sildenafil was stopped (no data or analysis reported). Healing of ulceration did not occur during treatment with placebo. The secondary outcome of mean Raynaud's Condition Score, which is commonly used to assess the impact of Raynaud's symptoms on a person's day-to-day life (Merkel et al. 2002), was also statistically significantly lower with sildenafil compared with placebo, although it is not clear if this was a clinically significant effect.

Herrick et al. (2011) was a multicentre European study that included 57 people with Raynaud's phenomenon secondary to limited cutaneous systemic sclerosis. People in the study were randomised to receive modified-release sildenafil (n=30, initially 100 mg once daily for 3 days then increased to 200 mg once daily for 25 days) or placebo (n=27) for 28 days. The per-protocol population consisted of 45 people (sildenafil, n=20; placebo, n=25) who received all treatments, completed diaries, and did not violate the protocol. The authors reported that modified-release sildenafil 200 mg once daily is similar to 50 mg of immediate-release sildenafil 3 times daily. The primary outcome was the change in the number of Raynaud's phenomenon attacks per week. Secondary outcomes included Raynaud's Condition Score, Raynaud's phenomenon pain score and mean duration of Raynaud attacks. Eight people (3 in the placebo group and 5 in the sildenafil group) had digital ulcers at baseline (Herrick et al. 2009).

The primary outcome, the mean percentage change from baseline to week 4 in the number of Raynaud attacks per week, was statistically significantly greater for modified-release sildenafil than for placebo in the per-protocol population (−44.0% compared with −18.1% respectively; p=0.034). Although improvement in the mean number of attacks per week was reported in both groups, this was not statistically significantly different between groups (p=0.244). Differences between groups in the secondary outcomes of Raynaud's Condition Score pain score and mean duration of attacks were not statistically significant.

The effect of sildenafil on digital ulceration improvement and healing was an exploratory outcome in Herrick et al. (2011). Some data on digital ulcer healing were reported in an abstract (Herrick et al. 2009). The number of people with digital ulcers improved with modified-release sildenafil from 5 (25%) at baseline to 4 (20%) at day 14 and to 3 (15%) at day 28. In the placebo group, the number of people with digital ulcers was 3 (12%) at baseline, 4 (16%) at day 14, and 5 (20%) at day 28 (no analysis reported).

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The authors of the meta-analysis (Tingey et al. 2013) reported statistical data extraction and recalculation with 95% confidence intervals (CI) for digital ulcer healing and prevention in the studies they included. They reported non-statistically significant relative risks (RR) of 5.00 (95% CI 0.29 to 86.43; p=0.27) for digital ulcer healing and 13.00 (95% CI 0.89 to 89.39; p=0.06) for digital ulcer improvement with sildenafil compared with placebo in Fries et al. (2005), and a non-statistically significant RR of 3.33 (95% CI 0.21 to 52.68; p=0.39) for digital ulcer healing with sildenafil compared with placebo in Herrick et al. (2011).

The meta-analysis pooled effect for PDE5 inhibitors as a class did show a statistically significant benefit compared with placebo for digital ulcer healing (RR 3.28, 95% CI 1.32 to 8.13, p=0.01) and digital ulcer improvement (RR 4.29, 95% CI 1.73 to 10.66, p=0.002 [Tingey et al. 2013]). However, the pooled effect also included data from a crossover study evaluating tadalafil (n=24, Shenoy et al. 2010) and therefore this result may not be valid when specifically considering the effect of sildenafil for treating digital ulcers.

A small, prospective, single-centre pilot study evaluated the effect of sildenafil on digital ulcer healing in people with systemic sclerosis (n=19; Brueckner et al. 2010). In this study, 16 people with 49 digital ulcers refractory to standard treatment were treated with maximally tolerated doses of sildenafil (up to 150 mg per day) for up to 6 months. Three people did not receive sildenafil for more than 1 month and were excluded from the analysis. The primary outcome was digital ulcer healing. Secondary end points included effects on Raynaud's phenomenon by using a visual analogue scale (VAS), the prevention of new ulcers, changes in VAS scores for pain, activity and experiencing ulcers, and the occurrence of sildenafil-related adverse effects. This study did not include a control group and, therefore, is not discussed in detail in this evidence summary. However, it does provide some data on the efficacy and safety of sildenafil as a treatment for digital ulcers, assessed as a primary outcome and over a longer period of time than the small RCTs.

The pilot study reported that 16 people (mean 3.1 ulcers per person at baseline) were treated with a mean sildenafil dose of 114 mg per day for a mean duration of 5.2 months (Brueckner et al. 2010). There was a statistically significant improvement in the number of digital ulcers at the end of sildenafil treatment (mean 1.1 ulcers per person). In all, 49 digital ulcers were present at baseline. During sildenafil treatment, 9 people developed 12 new ulcers between them. At the end of the study 17 ulcers were present (p<0.001 compared to baseline). Secondary outcomes for pain and activity statistically significantly improved during sildenafil treatment (p=0.002 and p=0.05 respectively).

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Safety and tolerability

In the meta-analysis (Tingey et al. 2013), the authors report that there were significant serious adverse events with PDE5 inhibitors, although these are not described as such in the individual trials; 7 people from the 3 trials (1 tadalafil study [n=24, Shenoy et al. 2010] and 2 sildenafil studies [n=20, Fries et al. (2005); and n=57, Herrick et al. 2011]) withdrew as a result of potential treatment-related adverse events, including headaches, myalgia, non-painful erections, allergic reaction, chest pain, palpitations, and facial oedema.

Across both sildenafil RCTs (Fries et al. 2005 and Herrick et al. 2011) more people in the sildenafil groups experienced adverse events (60% in Fries et al. 2005, and 93% in Herrick et al. 2011) compared with the placebo groups (0% in Fries et al. 2005, and 59% in Herrick et al. 2011). However, the investigators stated that most adverse events were transient (Fries et al. 2005) and mild or moderate and not unexpected for treatment with PDE5 inhibitors (Herrick et al. 2011). The most common adverse event for people taking sildenafil was headache (20% in Fries et al. 2005, and 50% in Herrick et al. 2011). Other less frequent adverse events included dyspepsia, arthralgia and myalgia. No statistical analysis relating to adverse events was reported in either RCT. Two people (10%) in Fries et al. (2005) and 4 people (13%) in Herrick et al. (2011) stopped taking sildenafil because of treatment-related adverse effects (mainly headache and myalgia). No deaths or serious adverse events were reported in the individual studies and the effect of sildenafil on blood pressure and heart rate was small (Herrick et al. 2011) or non-significant (Fries et al. 2005).

In the observational study (n=19, Brueckner et al. 2010), mild adverse effects were reported in 47% of participants, which caused 2 people to stop treatment. No statistical analysis was reported on adverse effects but the most commonly reported were palpitations, 21% (4/19); facial flushing, 21% (4/19); peripheral oedema, 16% (3/19); dyspnoea (breathlessness), 5% (1/19) and reoccurrence of atrial fibrillation, 5% (1/19). In 3 people with hypertension, the antihypertensive treatment was reduced during sildenafil treatment.

The summary of product characteristics for the sildenafil product that is licensed for managing pulmonary hypertension (Revatio) advises caution in people with certain underlying conditions which could be adversely affected by sildenafil's mild-to-moderate vasodilatory effects (for example, people with hypotension, fluid depletion, severe left ventricular outflow obstruction or autonomic dysfunction). Post-marketing data for sildenafil for male erectile dysfunction has reported serious adverse cardiovascular events. However, most of these people had pre-existing cardiovascular risk factors and many events were reported to occur during or shortly after sexual intercourse or occurred shortly after the use of sildenafil without sexual activity. Sildenafil is

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contraindicated in people with severe hypotension, or a recent history of stroke or myocardial infarction.

See the summaries of product characteristics for licensed sildenafil products for further information on contraindications, potential interactions and adverse effects of sildenafil.

Evidence strengths and limitations

Systemic sclerosis is a rare condition and RCTs are difficult to fund and recruit significant numbers of participants to. Data relating to the effect of sildenafil on digital ulceration are therefore very limited. Large prospective studies comparing sildenafil with placebo or other treatments that specifically consider digital ulcers as a primary outcome have yet to be published (Roustit et al. 2013). Studies with few events, such as those with small numbers of participants or those that run for short periods of time, limit the statistical power of the study to be able to detect differences in efficacy outcomes. As pointed out by the authors of the meta-analysis (Tingey et al. 2013), the 2 RCTs looking at sildenafil (Fries et al. 2005 and Herrick et al. 2011) were underpowered to detect a statistically significant difference between the sildenafil and placebo groups for digital ulcer healing and improvement and larger studies are needed. Small participant numbers also limit the safety data that these studies can provide. Less common adverse effects could have been missed and in observational studies, such as Brueckner et al. (2010), adverse effects may not have been recorded in detail for all participants.

Other limitations highlighted in the literature include a requirement to define and standardise digital ulcer indicators and end points (Steen et al. 2009). For example, in the 2 RCTs included in this evidence summary (Fries et al. 2005 and Herrick et al. 2011), investigators did not report the classification of partial ulcer healing versus fully healed ulcer, or stipulate methodology for measuring the depth and size of ulcers. The authors of the meta-analysis reported that these factors could affect the validity of results (Tingey et al. 2013). They also highlighted that randomisation was not stratified according to baseline ulcer presence or absence, which is a potential bias. Disease heterogeneity and baseline characteristics of study populations may have some bearing on treatment effect. For example, most published studies focus on the management of Raynaud's phenomenon as a primary outcome and the study population may include a mix of people with primary or secondary Raynaud's as in Fries et al. (2005). Additionally, smoking is associated with digital vascular disease in people with systemic sclerosis and investigators suggest that this should be taken into account in study design and data analysis (Herrick et al. 2011).

There are other limitations highlighted in the studies considered in this evidence summary. In Fries et al. (2005), blinding was compromised because all participants correctly identified whether they

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were receiving sildenafil or placebo. This may explain why no adverse effects were reported in the placebo treatment periods. Originally, 20 people were recruited to participate in the study but 2 people discontinued because of treatment-related adverse effects. The data analysis was, therefore, not an intention-to-treat analysis, and the observed effect estimate on the incomplete data set may be biased.

The 2 RCTs (Fries et al. 2005 and Herrick et al. 2011) used different doses of sildenafil, and data on the effective dose for preventing and healing digital ulcers are limited. The modified-release sildenafil 100 mg tablet used in Herrick et al. (2011) is not available in the UK.

The uncontrolled study (Brueckner et al. 2010) provides some observational data on maximally tolerated doses and showed a statistically significant benefit of sildenafil for the primary patient-oriented outcome of ulcer healing. However, all observational studies have limitations inherent in their non-randomised design, particularly around selection bias. The characteristics of the participants selected for treatment with sildenafil in these studies may have differed from the wider population of people with systemic sclerosis from which they were drawn, which could have affected the outcomes. Other limitations of this observational study are the small numbers of participants and the absence of a control group. In addition, the paper did not provide detailed information on digital ulcer definition and how this was assessed.

Context and estimated impact for the NHS

Cost effectiveness

No cost-effectiveness studies were identified that assessed using sildenafil off-label for managing digital ulcers.

The table below gives costs for some of the drugs used in Raynaud's phenomenon and digital ulcers associated with systemic sclerosis as recommended by the European League against Rheumatism (EULAR) Scleroderma Trials and Research group in 2009 (Kowal-Bielecka et al. 2009). Only bosentan is licensed specifically for preventing digital ulcers in people with systemic sclerosis and pre-existing ulcers (it has not been shown to heal existing digital ulcers). Iloprost injection is unlicensed in the UK but can be supplied on request from the manufacturer. Iloprost is given by infusion, which involves admission to hospital as either a day case or as an inpatient. None of the other drugs is licensed specifically for use in people with digital ulcers and use of any of these would be off-label.

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The Department of Health has amended regulations to allow unrestricted prescribing of generic sildenafil for men with erectile dysfunction.

Table 1 Costs of drugs used in digital ulcers

	Usual dose[a]	Estimated cost for 28 days (or 1 treatment cycle[b]) excluding VAT
Sildenafil (oral)	20 mg or 25 mg 3 times daily increasing to 50 mg 3 times daily	20 mg 3 times daily=£416.58[c] 25 mg to 50 mg 3 times daily=£22.89 to £23.73[d]
Tadalafil (oral)	10 mg on alternate days up to 20 mg daily	£54.99 to £188.93[d]
Iloprost (intravenous)	3-5 days 0.5 nanograms to 2 nanograms/kg/minute for 6 hours	£425 to £475 drug costs per 5-day course, plus hospital costs[b]
Bosentan (oral)	62.5 mg twice daily for 4 weeks then 125 mg twice daily	£1510.21[c]
Nifedipine modified release (oral)	10 mg up to 40 mg twice daily	£3.64 to £10.10[d]

[a] Doses taken from the summaries of product characteristics and expert consensus opinion. With the exception of bosentan, none of these drugs is licensed specifically for digital ulcers and use would be off-label or, in the case of iloprost, unlicensed. The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.

[b] Iloprost injection is an unlicensed product in the UK and can be supplied on request from the manufacturer. No costs could be obtained from standard published sources or the manufacturer. Informal sources suggest that the cost is around £85 to £95 for a single 50 microgram ampoule (excluding VAT). This does not include associated costs of hospital inpatient or day case admission.

[c] Costs taken from MIMS, February 2015. Costs are excluding VAT.

[d] Costs taken from the Drug Tariff, February 2015. Costs are excluding VAT.

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Current drug usage

No estimate of the current UK use of off-label sildenafil for treating digital ulcers was available at the time this evidence summary was prepared.

Information for the public

A plain English summary is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with digital ulcers who are thinking about trying sildenafil.

Relevance to NICE guidance programmes

There is currently no NICE guidance on managing digital ulcers or systemic sclerosis. Sildenafil for managing digital ulcers is not currently planned into any other NICE work programme. NICE has issued guidance that includes recommendations on sildenafil for managing erectile dysfunction, its licensed indication.

NICE has also issued guidance on idiopathic pulmonary fibrosis. This includes sildenafil in a list of drugs that are not recommended for use, either alone or in combination, to modify disease progression in idiopathic pulmonary fibrosis.

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Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Dr Anderson has received honoraria and been on advisory boards for Actelion pharmaceuticals. She is also the Merseyside and Cheshire Senate member on the NHS England Specialised Rheumatology Clinical Reference Group and co-authored the 2015 Clinical commissioning policy: sildenafil and bosentan for the treatment of digital ulceration in systemic sclerosis.

Professor Bruce has received consulting fees and research grants from: UCB, GSK, Roche, Medimmune, Genzyme/Sanofi and Pfizer and speaker fees from UCB, Roche and GSK.

Professor Denton has been an investigator in clinical trials of sildenafil and bosentan. He also chairs the UK Scleroderma Study Group and is part of the EULAR Scleroderma recommendations group. He has been a consultant to Pfizer (not currently) and Actelion (current) to advise about management of digital ulcers and Raynaud's phenomenon.

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About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance**.

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