

# Pulmonary sarcoidosis: infliximab

Evidence summary

Published: 20 December 2016

[www.nice.org.uk/guidance/es2](http://www.nice.org.uk/guidance/es2)

## Key points from the evidence

The content of this evidence summary was up-to-date in December 2016 . See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Summary

A randomised controlled trial (RCT) found that, in 138 people with **stable** pulmonary sarcoidosis, infliximab improved mean percent of predicted forced vital capacity (FVC) at week 24 by 2.5% compared with placebo; this was statistically significant. However, although some individual patients with stable disease, especially those with more severe symptoms, may see greater benefits, it is unclear whether this small, average improvement in this disease-oriented outcome is clinically important on a population basis. There were no statistically significant differences between infliximab and placebo in health-related quality of life, dyspnoea and 6-minute walking distance at week 24.

Three uncontrolled, non-comparative observational studies in a total of 60 people with **refractory** pulmonary sarcoidosis found that infliximab improved mean percent of predicted FVC or vital capacity (VC, not forced) from baseline by about 7%. Across these studies, improvements were also seen in other lung function outcomes, markers of disease activity and quality of life. The results suggest that infliximab may be effective in a small subset of people with active, unstable pulmonary sarcoidosis for whom corticosteroids and other treatments have proven ineffective or who cannot tolerate these treatments (refractory pulmonary sarcoidosis), in whom life expectancy may be reduced. However, observational studies have many limitations and better quality evidence is needed to confirm this.

Adverse events seen in the studies reflected those listed in the summary of product characteristics.

The evidence supports British Thoracic Society (BTS) guidance that immunosuppressants such as infliximab have only a limited role in pulmonary sarcoidosis because there are insufficient high-quality studies to confirm their place in therapy and they have significant adverse effects. The guidance advises that immunosuppressants should be used only when disease is refractory to standard treatments and when there are no pharmacological alternatives.

**Regulatory status:** Use of infliximab for treating any manifestation of sarcoidosis is off-label.

At the time of publication, 4 infliximab products are available: the original brand Remicade, and 3 biosimilar medicines, Flixabi, Inflectra and Remsima.

Effectiveness	Safety
<ul style="list-style-type: none"> <li>• The <a href="#">Baughman et al. (2006)</a> RCT found that infliximab (n=93) improved mean % predicted FVC at week 24 by 2.5% compared with placebo (n=45, p=0.038) in people with <b>stable</b> pulmonary sarcoidosis; this was statistically significant.</li> <li>• There were no statistically significant differences between the groups in health-related quality of life, dyspnoea and 6-minute walking distance at week 24.</li> <li>• In subsets of people with <b>refractory</b> pulmonary sarcoidosis in non-comparative observational studies by <a href="#">Vorselaars et al. (2015)</a> (n=28), <a href="#">Ørum et al. (2012)</a> (n=9) and <a href="#">Van Rijswijk et al. (2013)</a> (n=23) respectively, infliximab improved mean % predicted: <ul style="list-style-type: none"> <li>– FVC by 6.6% at 26 weeks (p=0.0007)</li> <li>– FVC by 7.1% at 25 months (p value not reported)</li> <li>– VC by 7.6% at 18 weeks (p&lt;0.0001).</li> </ul> </li> </ul> <p>These results are statistically</p>	<ul style="list-style-type: none"> <li>• The most serious adverse effects that have been reported with infliximab include hepatitis B virus reactivation, congestive heart failure, serious infections (including sepsis, opportunistic infections and tuberculosis) and serious infusion reactions. Sarcoidosis and sarcoid-like reactions have been reported rarely. See the <a href="#">Remicade summary of product characteristics</a> for a complete list.</li> <li>• In <a href="#">Baughman et al. (2006)</a>, serious adverse events were reported in 8/44 people (18%) in the placebo group and 21/91 people (23%) in the infliximab group.</li> <li>• In <a href="#">Baughman et al. (2006)</a>, the most commonly reported adverse effects were upper respiratory tract infection, coughing, dyspnoea and pain (sarcoidosis, bronchitis, headache and back pain).</li> <li>• In <a href="#">Vorselaars et al. (2015)</a>, 2 people died and 13/56 people (22%) had mild adverse effects. In <a href="#">Russell et al. (2013)</a>, 15/26 people (58%) had adverse effects. Few adverse effects were reported in the other observational studies.</li> <li>• Adverse events seen in the studies reflected those listed in the <a href="#">summary of product characteristics</a>.</li> </ul>

<p>significant.</p> <ul style="list-style-type: none"><li>• An increase in mean % predicted FVC of more than 10% was seen in 13/28 people in <u>Vorselaars et al. (2015)</u>, and an increase in mean % predicted VC of more than 10% was seen in 12/23 people in <u>Van Rijswijk et al. (2013)</u> (p values not reported).</li><li>• Improvements were also seen in other measures of lung function and markers of disease activity.</li><li>• A further study by <u>Russell et al. (2013)</u> (n=15), found no statistically significant differences in lung function outcomes.</li></ul>	
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Patient factors	Resource implications
<ul style="list-style-type: none"> <li>In <a href="#">Baughman et al. (2006)</a>, 2/44 people taking placebo and 5/91 people taking infliximab discontinued treatment due to adverse events.</li> <li>8/56 patients in <a href="#">Vorselaars et al. (2015)</a>, 2/12 people in <a href="#">Ørum et al. (2012)</a> and 3/26 patients in <a href="#">Russell et al. (2013)</a> discontinued infliximab due to adverse effects.</li> <li>Patients should be tested for hepatitis B virus and active and latent tuberculosis before starting treatment (<a href="#">Remicade summary of product characteristics</a>).</li> <li>Patients must be monitored closely for infections including tuberculosis before, during and 6 months after treatment with infliximab (<a href="#">Remicade summary of product characteristics</a>).</li> </ul>	<ul style="list-style-type: none"> <li>One vial of infliximab 100 mg powder for concentrate for solution for infusion costs £419.62 for Remicade, £377.66 for Inflectra or Remsima and £377.00 for Flixabi without discounts (<a href="#">MIMS</a>, October 2016).</li> <li>A course of infliximab as given in <a href="#">Baughman et al. (2006)</a> costs about £7,000 to £10,000 for an 80 kg person.</li> <li>These costs are for the medicine only and do not include VAT, any local procurement discounts or other costs incurred, such as dilution and administration or standard supportive therapy.</li> <li>At the time of publication, 4 infliximab products are available: the original brand <a href="#">Remicade</a>, and 3 biosimilar medicines, <a href="#">Flixabi</a>, <a href="#">Inflectra</a> and <a href="#">Remsima</a>. For more information see the <a href="#">NICE Key therapeutic topic on biosimilar medicines</a>.</li> </ul>

## Introduction and current guidance

The cause of sarcoidosis is unknown, although it may be due to an inflammatory response to an environmental agent or infection. It is characterised by the presence of non-caseating granulomas (non-necrotising nodules of inflammation and scarring) in the organs. The lungs are affected in more than 90% of people with sarcoidosis (Sarcoidosis, [Oxford Textbook of Medicine](#)).

Sarcoidosis can present in a wide variety of ways, ranging from mild, acute self-limiting disease to chronic disease involving several organs and causing severe symptoms and functional impairment. The prognosis is generally good and sarcoidosis resolves in most people within 2 to 5 years; however, about 25% of people will develop residual fibrosis in the lungs or elsewhere. Disease-related mortality is reported to be about 5%, with the most common causes of death being from lung, cardiac and neurological disease that is refractory to therapy (Sarcoidosis, [Oxford Textbook of Medicine](#)).

Because of the high rates of spontaneous remission, treatment is not recommended for people with no or mild symptoms. If treatment is needed, corticosteroids are recommended first-line. The BTS advises that other immunosuppressive or anti-inflammatory treatments have only a limited role in sarcoidosis. However, such treatments should be considered if corticosteroids do not control the disease or have intolerable adverse effects. There is some evidence to support the use of methotrexate as a steroid-sparing agent and this is recommended as the immunosuppressant of choice for pulmonary sarcoidosis. Lung transplantation should be considered in end stage pulmonary sarcoidosis ([BTS Interstitial lung disease guideline 2008](#)).

This evidence summary considers the best available evidence for infliximab for treating pulmonary sarcoidosis. A related evidence summary has considered infliximab for [extrapulmonary sarcoidosis](#).

[Full text of introduction and current guidance.](#)

## Product overview

Infliximab is a biological human monoclonal antibody, which inhibits tumour necrosis factor (TNF) alpha (a cell signalling protein or cytokine involved in systemic inflammation) reducing disease activity ([Remicade summary of product characteristics](#)).

At the time of publication, 4 infliximab products are available: the original brand [Remicade](#), and 3 biosimilar medicines, [Flixabi](#), [Inflectra](#) and [Remsima](#). For more information see the [NICE Key therapeutic topic on biosimilar medicines](#), which provides links to other resources including [answers to commonly asked questions about biosimilar versions of infliximab](#).

Infliximab is licensed for treating rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis ([Remicade summary of product](#)

characteristics). Use of infliximab for treating any manifestation of sarcoidosis is off-label.

Full text of product overview.

## Evidence review

- This evidence summary includes 1 randomised controlled trial (RCT) and 4 observational studies.
- The RCT by Baughman et al. (2006) compared infliximab 3 mg/kg and infliximab 5 mg/kg with placebo in 138 people with chronic, **stable** pulmonary sarcoidosis who were taking regular doses of corticosteroids and/or immunosuppressants.
- The RCT found that infliximab (3 mg/kg and 5 mg/kg combined, n=93) improved percent of predicted forced vital capacity (FVC) at week 24 by 2.5% compared with placebo (n=45,  $p=0.038$ ); this was statistically significant. There were no statistically significant differences between infliximab and placebo in health-related quality-of-life scores or dyspnoea scores at weeks 24 or 52. There were also no differences between the groups in 6-minute walking distance at week 24.
- A prospective non-comparative study by Vorselaars et al. (2015) and 3 case series by Ørum et al. (2012), Russell et al. (2013) and Van Rijswijk et al. (2013) considered infliximab (usually 3–5 mg/kg) for treating people with chronic sarcoidosis in their lungs or other organs who either had a suboptimal response to the usual treatments, or who could not tolerate those treatments (**refractory** sarcoidosis). In subsets of people with pulmonary sarcoidosis, infliximab statistically significantly improved:
  - Mean percent predicted FVC by 6.6% at 26 weeks in Vorselaars et al. (2015) (n=28,  $p=0.0007$ , 8 treatments). An increase of more than 10% was seen in 13/28 people (p value not reported).
  - Mean percent predicted FVC by 7.1% at 25 months in Ørum et al. (2012) (n=9, p value not reported, mean 15 treatments).
  - Mean percent predicted vital capacity (VC, not forced) by 7.6% at 18 weeks in Van Rijswijk et al. (2013) (n=23,  $p<0.0001$ , 6 treatments). An increase of more than 10% was seen in 12/23 people (p value not reported).

In these studies, improvements were also seen in other lung function outcomes and in markers of disease activity and inflammation.

- No statistically significant differences in lung function outcomes were seen in the study by [Russell et al. \(2013\)](#). However, when objective clinical outcomes (such as imaging) were used, pulmonary sarcoidosis resolved or improved in 8/15 people (p value not reported, mean duration 46 months, about 36 treatments). This study mainly included African-American people; sarcoidosis is more severe and difficult to treat in this population.
- The adverse events seen in the studies reflect those listed in the [Remicade summary of product characteristics](#). According to the summary of product characteristics, in clinical trials of infliximab for the licensed indications, upper respiratory tract infection was the most common adverse drug reaction (25.3% with infliximab compared with 16.5% with control). Other very common adverse effects (occurring in 1 in 10 patients or more) include viral infections (such as influenza and herpes virus infection), headache, sinusitis, abdominal pain, nausea, generalised pain and infusion-related reactions. The most serious adverse drug reactions that have been reported with infliximab include hepatitis B virus reactivation, congestive heart failure, serious infections (including sepsis, opportunistic infections and tuberculosis) and serious infusion reactions. Sarcoidosis and sarcoid-like reactions have been reported rarely. See the [summary of product characteristics](#) for a complete list.
- In the RCT by [Baughman et al. \(2006\)](#), 2/44 people taking placebo and 5/91 people taking infliximab discontinued treatment due to adverse events. In [Vorselaars et al. \(2015\)](#), 8/56 patients discontinued infliximab (2 of whom died) and in [Russell et al. \(2013\)](#) 3/26 discontinued infliximab. No treatment discontinuations were reported in the other studies.
- The studies have many limitations affecting their application to clinical practice. Although [Baughman et al. \(2006\)](#) found that infliximab statistically significantly improved the disease-oriented primary outcome (mean percent predicted FVC) at 24 weeks compared with placebo, it is unclear whether the small, average improvement was [clinically important](#). Also, there were no statistically significant differences in any of the major patient-oriented outcomes at 24 weeks. All patients in the study by [Baughman et al. \(2006\)](#) were taking stable background corticosteroid and/or immunosuppressant therapy. Also, sarcoidosis did not need to be active or refractory to treatment. From this RCT, it is not known whether infliximab would be more effective in the small subset of people with active, refractory pulmonary sarcoidosis, in whom life expectancy may be reduced.



- The uncontrolled [observational studies](#) in this evidence summary were undertaken in people with refractory sarcoidosis, and the improvement in percent of predicted FVC seen in the observational studies was generally higher than in the RCT by [Baughman et al. \(2006\)](#) (around 7%, compared with 2.5%). However, observational studies are more subject to [bias](#) and [confounding](#) than RCTs. Also, as is usual for a rare disease, all the studies had small [sample sizes](#).
- Disease-oriented outcomes were primarily used in the observational studies. [Van Rijswijk et al. \(2013\)](#) and [Vorselaars et al. \(2015\)](#) did find some statistically significant improvements in health-related quality of life in people with sarcoidosis in their lungs or other organs. However, these improvements did not always reach the level considered to be clinically important. Although improvements in FVC or VC and other lung function outcomes were seen in most of the studies, the minimal clinically important changes for sarcoidosis are unclear. Nevertheless, some patients seem to have seen substantial benefits and, in people with severe and active refractory disease, even stabilisation of lung function may be preferable to further deterioration.
- The evidence supports [BTS guidance](#) that immunosuppressants such as infliximab have only a limited role in pulmonary sarcoidosis because there are insufficient high-quality studies to confirm their place in therapy and they have significant adverse effects. The guidance advises that immunosuppressants should be used only when disease is refractory to standard treatments and when there are no pharmacological alternatives.

[Full text of evidence review.](#)

## Context and estimated impact for the NHS

According to [MIMS](#) (October 2016), 1 vial of infliximab 100 mg powder for concentrate for solution for infusion costs £419.62 for Remicade, £377.66 for Inflectra or Remsima and £377.00 for Flixabi (excluding VAT). Using these products, the cost of a course of infliximab treatment based on the doses of infliximab and treatment regimens used in the study by [Baughman et al. \(2006\)](#) (3 mg/kg or 5 mg/kg at weeks 0, 2, 6, 12, 18 and 24) ranges from about £7,000 to £10,000 for an 80 kg person (see table 3 in [full text of context and estimated impact for the NHS](#) for more information). However, these costs are for the medicine only (excluding VAT) and do not include any local procurement discounts or other costs incurred, such as dilution and administration or standard supportive therapy.

[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 sarcoidosis who are thinking about trying infliximab.

### 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.**

## Full evidence summary

### Introduction and current guidance

The cause of sarcoidosis is unknown, although it may be due to an inflammatory response to an environmental agent or infection. In the UK, the incidence of the condition is estimated to be about 3/100,000 person-years, based on general practice data ([British Thoracic Society \[BTS\] Interstitial lung disease guideline 2008](#)).

Sarcoidosis can present in a wide variety of ways, ranging from mild, acute self-limiting disease to chronic disease involving several organs and causing severe symptoms and functional impairment. It is characterised by the presence of non-caseating granulomas (non-necrotising nodules of inflammation and scarring) in the organs. The lungs are affected in more than 90% of people with sarcoidosis and the disease can be staged according to the appearance of the lungs on a chest X-ray:

- stage 1, hilar adenopathy alone (enlargement of the lymph nodes within the lung hilum, where the bronchus, blood vessels and nerves enter)
- stage 2, adenopathy and parenchymal (the functional tissue of the lung) disease
- stage 3, parenchymal disease alone
- stage 4, fibrosis.

The skin is the second most commonly affected organ. Other organs such as the eyes, brain, nervous system, liver and heart may also be affected. There are significant differences in the severity of disease and organs involved depending on the ethnicity of the patient (Sarcoidosis, [Oxford Textbook of Medicine](#)).

The prognosis is generally good and sarcoidosis resolves in most people within 2 to 5 years; however, about 25% of people will develop residual fibrosis in the lungs or elsewhere. Disease-related mortality is reported to be about 5%, with the most common causes of death being from lung, cardiac and neurological disease that is refractory to therapy (Sarcoidosis, [Oxford Textbook of Medicine](#)). African-Americans with sarcoidosis tend to have more aggressive disease and a poorer prognosis ([BTS Interstitial lung disease guideline 2008](#)).

According to the [BTS guideline on interstitial lung disease](#) (accredited by [NICE](#)), a number of factors need to be taken into account before treatment is considered for pulmonary sarcoidosis. Firstly, spontaneous remission occurs in 55–90% of people with stage 1 disease, 40–70% with stage 2 disease and 10–20% with stage 3 disease, usually within the first 6 months. Secondly, the natural history of the condition varies and it is difficult to predict the course and prognosis. Finally, the long-term effects of treatment need to be taken into account.

Because of the high rates of spontaneous remission, treatment is not recommended by BTS for:

- asymptomatic stage 1 pulmonary sarcoidosis
- asymptomatic stage 2 or 3 pulmonary sarcoidosis with mildly abnormal lung function and stable signs and symptoms.

An oral corticosteroid such as prednisolone is recommended first-line for:

- progressive lung disease determined by radiology
- significant symptoms of pulmonary or extrapulmonary disease needing treatment.

The [BTS Interstitial lung disease guideline \(2008\)](#) advises that other immunosuppressive or anti-inflammatory treatments have only a limited role in sarcoidosis because, when the evidence was assessed in 2008, insufficient high-quality studies were found to confirm their place in therapy. However, the guideline advises that such treatments should be considered if corticosteroids do not control the disease or if the person experiences intolerable adverse effects. There is some evidence to support the use of methotrexate as a steroid-sparing agent and this is recommended as the immunosuppressant of choice for pulmonary sarcoidosis.

Other treatment options that have been used for sarcoidosis include ciclosporin, hydroxychloroquine, azathioprine, chlorambucil, cyclophosphamide, leflunomide, pentoxifylline, thalidomide, infliximab and etanercept. The [BTS guideline](#) notes that these medicines have significant adverse effects and, as there is limited good-quality evidence to support their use, advises that they should be used only when disease is progressing and there are no alternatives. Lung transplantation should be considered in end stage pulmonary sarcoidosis.

This evidence summary considers the best available evidence for infliximab for treating pulmonary sarcoidosis. A related evidence summary has considered infliximab for [extrapulmonary sarcoidosis](#).

## Product overview

### Drug action

Infliximab is a biological human monoclonal antibody, which inhibits tumour necrosis factor (TNF) alpha (a cell signalling protein or cytokine involved in systemic inflammation) reducing disease activity ([Remicade summary of product characteristics](#)).

### Regulatory status

Infliximab is licensed for treating rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis ([Remicade summary of product characteristics](#)). Use of infliximab for treating any manifestation sarcoidosis 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 infliximab outside its authorised indications. [Supporting information and advice](#) is also available from the GMC.

## Cost

At the time of publication, 4 infliximab products are available: the original brand [Remicade](#), and 3 biosimilar medicines, [Flixabi](#), [Inflectra](#) and [Remsima](#).

For more information see the [NICE Key therapeutic topic on biosimilar medicines](#), which provides links to other resources including [answers to commonly asked questions about biosimilar versions of infliximab](#).

According to [MIMS](#) (October 2016), 1 vial of infliximab 100 mg powder for concentrate for solution for infusion costs £419.62 for Remicade, £377.66 for Inflectra or Remsima and £377.00 for Flixabi (excluding VAT). However, these costs do not include any local procurement discounts or other costs incurred, such as dilution and administration or standard supportive therapy.

## Evidence review

This evidence summary is based on the best available evidence for infliximab for treating pulmonary sarcoidosis. It includes 1 [randomised controlled trial](#) (RCT: [Baughman et al. 2006](#)) and 4 observational studies (a [prospective study](#) by [Vorselaars et al. 2015](#) and 3 [case series](#) by [Ørum et al. 2012](#), [Russell et al. 2013](#) and [Van Rijswijk et al. 2013](#)).

A second RCT by [Rossman et al. \(2006\)](#) compared infliximab and placebo for treating chronic pulmonary sarcoidosis that was refractory to treatment. However, this study was excluded from the evidence summary because of severe limitations affecting its interpretation. Most importantly, it failed to recruit sufficient participants (only 19 of a planned 42) and was [statistically underpowered](#) to detect any differences between the groups, should any exist.

## Randomised controlled trial

[Baughman et al. 2006](#)

- Design: This study was a randomised, double-blind, placebo-controlled phase II study in 34 centres in the US and Europe. It evaluated the efficacy of infliximab for treating chronic, stable sarcoidosis with pulmonary involvement.
- Patients: Patients were included if they had histologically proven sarcoidosis for at least 1 year (mean 7 years), evidence of parenchymal disease on chest X-ray, a forced vital capacity (FVC) of 50% to 85% of the predicted value (mean 69%), a Medical Research Council dyspnoea score of at least grade 1, and stable treatment with at least 10 mg daily of prednisone or equivalent (mean about 13 mg) or at least 1 immunosuppressant for at least 3 months. The medication regimens and doses were to remain stable during the study (51% received corticosteroids only, 7% received immunosuppressants only and 42% received both). Exclusion criteria included serious infection with 2 months of screening and opportunistic infection within 6 months of screening, and history of latent treated or untreated tuberculosis. Baseline characteristics were generally similar between the groups.
- Intervention and comparison: 138 patients (mean age 47 years, 67% white) were randomised 1:1:1 to receive intravenous infusions of placebo (n=45), infliximab 3 mg/kg (n=46) or infliximab 5 mg/kg (n=47) at weeks 0, 2, 6, 12, 18 and 24 and were followed up for 52 weeks. It is unclear if allocation was concealed.
- Outcomes: the primary end point was the change from baseline in the percent of predicted FVC at week 24. Major secondary end points included the St. George's Respiratory Questionnaire (SGRQ) total score (range 0 to 100, with higher scores indicating lower health-related quality of life: a change of 4 units is generally considered clinically important), Borg's CR10 dyspnoea score (range 0 to 10, with higher scores indicating worse dyspnoea) and 6-minute walk test (6-MWT) distance (with longer distances indicating better function). Other secondary outcomes included adverse events and assessment of sarcoidosis in extrapulmonary organs.

**Table 1 Summary of results for Baughman et al. 2006**

	Placebo	Infliximab 3 mg/kg	Infliximab 5 mg/kg	All infliximab	Analysis
Randomised	n=45	n=46	n=47	n=93	
<b>Efficacy</b>	n=45	n=46	n=47	n=93	

Primary outcome: change from baseline in % predicted FVC at week 24 (LS mean)	0.0%	2.8%	2.2%	2.5%	Versus placebo: 3 mg/kg: difference 2.8%, p=0.041 5 mg/kg: difference 2.2%, p=0.116, NS All infliximab: difference 2.5%, p=0.038
Selected secondary outcomes:					
Change from baseline in SGRQ total score at week 52 (LS mean ± SE)	-2.4±2.1	-2.9±2.2	-3.4±2.1	-3.1±1.6	Versus placebo 3 mg/kg: difference -0.5, NS 5 mg/kg: difference -1.0, NS All infliximab: difference -0.7, NS
Change from baseline in CR10 score at week 52 (LS mean ± SE)	0.7±2.4	0.5±2.2	0.1±2.1	0.3±2.1	Versus placebo 3 mg/kg: difference 0.2, NS 5 mg/kg: difference 0.6, NS All infliximab: difference 0.4, NS

Change from baseline in 6-MWT distance (metres) at week 52 (LS mean $\pm$ SE) <sup>a</sup>	-19.9 $\pm$ 9.4	17.1 $\pm$ 9.4	-1.8 $\pm$ 9.5	7.6 $\pm$ 6.6	Versus placebo 3 mg/kg: difference 37.0, p=0.007 5 mg/kg: difference 18.1, NS All infliximab: difference 27.5, p=0.019
<b>Safety</b> <sup>b</sup>	n=44	n=45	n=46	n=91	
Patients reporting serious adverse events at week 52	18.2% (8/44)	24.4% (11/45)	21.7% (10/46)	23.1% (21/91)	Statistical analysis not reported
Patients reporting adverse events at week 52	93.2% (41/44)	88.9% (40/45)	87.0% (40/46)	87.9% (80/91)	Statistical analysis not reported
Patients reporting infections that needed antimicrobial treatment at week 52	61.4% (27/44)	57.8% (26/45)	50.0% (23/46)	53.8% (49/91)	Statistical analysis not reported
Patients who discontinued treatment due to adverse events	4.5% (2/44)	Not reported	Not reported	5.5% (5/91)	Statistical analysis not reported
<p>Abbreviations: 6-MWT, <u>6-minute walk test</u> distance (with longer distances indicating better function); CR10, <u>Borg's CR10 dyspnoea score</u> (range 0 to 10, with higher scores indicating worse dyspnoea); FVC, forced vital capacity; LS, mean; NS, not significant; p, <u>p value</u>; SE, standard error; SGRQ, <u>St. George's Respiratory Questionnaire</u> (range 0 to 100, with higher scores indicating lower health-related quality of life: a change of 4 units is generally considered <u>clinically important</u>); URTI, upper respiratory tract infection.</p> <p><sup>a</sup> Uses last observation carried forward methodology.</p> <p><sup>b</sup> One patient in each group withdrew consent.</p>					



## Observational studies

**Table 2 Summary of non-comparative observational studies**

Study design	Patients	Interventions	Selected outcomes
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<p><u>Vorselaars et al. 2015</u></p> <p>Prospective, uncontrolled open-label study in the Netherlands</p> <p>Investigated infliximab for refractory sarcoidosis</p>	<p>56 patients (mean age 48 years, 87.5% white) with severe<sup>a</sup> sarcoidosis (mean duration 6.8 years, 80% stage 2–4) unresponsive to first- and second-line treatment<sup>b</sup> or who had had severe adverse effects from treatments<sup>c,d</sup>.</p> <p>In the total study population, stable or deteriorating pulmonary function was seen in the 6 months before infliximab was initiated.</p> <p>34 patients (61%) primarily had pulmonary sarcoidosis. 28 of these were treated for a pulmonary indication. At baseline, mean FVC was 73.6% predicted and mean SUV<sub>max</sub> in lung parenchyma was 9.0 (indicating high disease activity).</p>	<p>Infliximab 5 mg/kg at weeks 0 and 2 then every 4 weeks for 6 months (8 infusions).</p> <p>Prednisolone dose could be tapered.</p>	<p>At 26 weeks in the 28 patients with a pulmonary treatment indication:</p> <ul style="list-style-type: none"> <li>• Mean % predicted FVC improved by 6.6% (p=0.0007). An increase of more than 10% was seen in 46% of patients (p value not reported).</li> <li>• Mean SUV<sub>max</sub> of lung parenchyma improved by <math>-5.3 \pm 5.6</math> SD (mean at baseline 9.0, p value not reported: mean improvement in all patients <math>-3.9</math>, p&lt;0.0001).</li> </ul> <p>At 26 weeks in the total population, measures of health-related quality of life statistically significantly improved (mean PGA <math>-14.6</math> from baseline of 61.0, p&lt;0.0001: mean SF-36 <math>+8.2</math> from baseline of 40.6, p=0.009).</p> <p>At 26 weeks in 19 patients taking prednisolone, the mean daily dose decreased by 8.8 mg (p=0.001). No patients increased their</p>
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			<p>concomitant immunosuppressant dose.</p> <p>8 patients had severe adverse effects: 7 of these discontinued treatment and 2 later died. 1 person discontinued treatment for an undisclosed reason. 13 patients had mild adverse effects.</p>
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<p><u>Ørum et al. 2012</u> Retrospective case review in Denmark Investigated infliximab for refractory sarcoidosis</p>	<p>12 patients (mean age 34 years at diagnosis, 92% white) with sarcoidosis (mean duration 5.8 years, 75% stage 2–4) refractory to standard immunotherapy (n=2) or with intolerable adverse effects on standard therapy (n=2) or both (n=8). Treatments at baseline included prednisolone (n=12), methotrexate (n=11) and azathioprine (n=6). 9 patients had pulmonary sarcoidosis.</p>	<p>The initial infliximab dose was 5 mg/kg in 1 patient and 3 mg/kg in 11 patients (increased to 5 mg/kg in 2 patients) at weeks 0, 2 and 6. For most patients treatment was then administered 8-weekly (mean duration 25 months, mean number of treatments 15). Patients also received other immunosuppressants.</p>	<p>In patients with pulmonary sarcoidosis, measures of pulmonary function (including FEV<sub>1</sub>, FVC and TLC) improved following infliximab. For example, compared with baseline, mean % predicted FVC increased by:</p> <ul style="list-style-type: none"> <li>• 5.1%±3.8% SD after 7 treatments (n=5, p value not reported)</li> <li>• 7.1%±11.6% SD after the last dosage (n=9, p value not reported).</li> </ul> <p>No changes in pulmonary staging on X-ray were seen in these patients. Markers of disease activity were raised at baseline in 6/9 patients and became normal with treatment. 2 patients discontinued treatment due to adverse effects.</p>
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<p><u>Russell et al. 2013</u> Retrospective case review in the US Investigated infliximab for refractory sarcoidosis</p>	<p>26 patients (mean age 51 years, 81% African-American) with sarcoidosis (average duration 14.9 years, staging not reported) refractory to corticosteroids or DMARDs or both, or who could not tolerate these treatments. Previous treatments included corticosteroids (n=24), methotrexate (n=20) and hydroxychloroquine (n=23). 15 patients had pulmonary sarcoidosis.</p>	<p>The average maximum infliximab dose was 511 mg (range 300–1000 mg) given on average every 5.5 weeks (range 4–6 weeks). The average duration of treatment was 46.2 months.</p>	<p>After 46.2 months, in 15 patients, using objective clinical outcomes (such as imaging), pulmonary sarcoidosis:</p> <ul style="list-style-type: none"> <li>• resolved in 4</li> <li>• improved in 4</li> <li>• was unchanged in 5</li> <li>• progressed in 2.</li> </ul> <p>(p values not reported) No statistically significant differences were seen from baseline in FEV<sub>1</sub>, FVC or TLC (2%, 4% and 11% improvement respectively). Adverse effects were seen in 15/26 patients, 3 of whom discontinued infliximab.</p>
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<p><u>Van Rijswijk et al. 2013</u> Retrospective case review in the Netherlands Investigated infliximab for refractory sarcoidosis</p>	<p>45 patients (mean age 49 years, ethnicity not reported) with sarcoidosis (mean duration 7.6 years, 73% stage 2–4) refractory to regular medication or who had severe adverse effects with these medicines. Baseline treatments included prednisone (n=12) methotrexate (n=1) or both (n=30). 23 patients had pulmonary sarcoidosis<sup>e</sup>.</p>	<p>Infliximab 5 mg/kg at weeks 0, 2, 6, 10, 14 and 18. Methotrexate was also started in 8 patients.</p>	<p>In the total study population, after 18 weeks, statistically significant improvements were seen in markers of disease activity on F-FDG PET, lung function and health-related quality of life. In 23 patients with pulmonary sarcoidosis, the mean changes in % predicted VC and FEV<sub>1</sub> were 7.6% (p&lt;0.0001) and 7.9% (p&lt;0.0001) respectively. Improvements in VC and FEV<sub>1</sub> remained significant when the 8 patients newly taking methotrexate were excluded. VC improved by 10–20% in 8 patients and over 20% in 4 patients. FEV<sub>1</sub> improved by 10–20% in 5 patients and by over 20% in 7 patients. Infliximab was well-tolerated. 1 patient was hospitalised.</p>
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Abbreviations: 6-MWT, 6-minute walk test distance; DMARD, disease modifying anti-rheumatic drug; F-FDG PET, <sup>18</sup>F-fluorodeoxyglucose by positron emission tomography; FEV<sub>1</sub>, forced expiratory volume in the first second; FVC, forced vital capacity; PGA, patient global assessment, a measure of health-related quality of life (range 0–100 with higher scores indicating worse health); SD, standard deviation; SF-36, 36-item Short Form health survey (range 0 to 100 with lower scores indicating a worse level of functioning); SUV<sub>max</sub>, maximised standardised uptake value on F-FDG PET, a marker of disease activity and inflammation; TLC, total lung capacity; TNF tumour necrosis factor; VC, vital capacity (not forced).

<sup>a</sup> Based on loss of function (for example, lung function or cardiac function), impaired quality of life and disease activity on F-FDG PET at baseline.

<sup>b</sup> 93% of patients had used at least 2 immunosuppressant treatments (mainly corticosteroids, methotrexate and azathioprine); 13 patients had previously received TNF-alpha inhibitors.

<sup>c</sup> For example, worsening diabetes, psychological deterioration or liver function disorders.

<sup>d</sup> Exclusion criteria included vaccination within the previous 3 months, active or untreated latent tuberculosis and serious infections in the last 2 months.

<sup>e</sup> Severe dyspnoea on exertion or a decline in pulmonary function tests despite treatment with immunosuppressant medicines.

## Clinical effectiveness

### Randomised controlled trial

Baughman et al. (2006) found that, in people with stable pulmonary sarcoidosis who were taking regular doses of corticosteroids and/or immunosuppressants, infliximab (3 mg/kg and 5 mg/kg combined, n=93) improved mean percent of predicted FVC at week 24 by 2.5% compared with placebo (n=45, p=0.038); this was statistically significant. However, it is unclear whether this small, average improvement in this disease-oriented outcome is clinically important.

There were no statistically significant differences between infliximab and placebo in mean SGRQ total scores or Borg's CR10 dyspnoea scores at weeks 24 or 52. There were also no differences between the groups in mean 6-minute walking distance at week 24. However, at week 52, 6-minute walking distance improved in the infliximab 3 mg/kg and the

combined infliximab group (but not the 5 mg/kg group) compared with placebo ( $p=0.007$  and  $p=0.019$  respectively: see table 1 for more information); this was statistically significant.

## Observational studies

The prospective study by [Vorseelaars et al. \(2015\)](#) found that infliximab 5 mg/kg statistically significantly improved mean percent of predicted FVC by 6.6% in 28 people with refractory pulmonary sarcoidosis ( $p=0.0007$ ) at 26 weeks. An increase of more than 10% was seen in 13 people ( $p$  value not reported). Statistically significant improvements were also seen in other measures of pulmonary function (for example, mean percent of predicted FEV<sub>1</sub> 5.8%,  $p<0.0001$ ) and in markers of disease activity and inflammation (for example, mean SUV<sub>max</sub> of the lung parenchyma  $-5.3$ ,  $p$  value not reported). Measures of health-related quality of life statistically significantly improved in the total study population with refractory sarcoidosis in their lungs or other organs ( $n=56$ ). See table 2 for more information.

In this study, the authors reported that baseline pulmonary function tests did not predict treatment outcome. In people with refractory pulmonary sarcoidosis, baseline SUV<sub>max</sub> of the lung parenchyma was associated with percent predicted FVC, with a high SUV<sub>max</sub> associated with a better response to treatment.

The retrospective case review by [Ørum et al. \(2012\)](#) found that pulmonary function improved with infliximab (3 or 5 mg/kg) in 9 people with refractory pulmonary sarcoidosis. Compared with baseline, mean percent of predicted FVC increased by 5.1% after 7 treatments ( $n=5$ ,  $p$  value not reported) and 7.1% after the last dosage ( $n=9$ ,  $p$  value not reported, mean treatment duration 25 months). No changes were seen in pulmonary staging on X-ray. In 6 patients with raised markers of disease activity at baseline, mean values became normal with treatment.

In their retrospective case review of people (81% African-American) with refractory sarcoidosis treated with infliximab (average dose 511 mg), [Russell et al. \(2013\)](#) found mixed results for pulmonary sarcoidosis. When objective clinical outcomes (such as imaging) were used, the disease resolved or improved in 8 out of 15 people after a mean treatment duration of 46 months ( $p$  value not reported). In 2 people, pulmonary sarcoidosis worsened. No statistically significant differences from baseline were seen in FEV<sub>1</sub>, FVC or TLC (2%, 4% and 11% improvement respectively).

In 23 patients with refractory pulmonary sarcoidosis treated with infliximab 5 mg/kg in the



retrospective case review by [Van Rijswijk et al. \(2013\)](#), mean percent predicted vital capacity (VC, not forced) and FEV<sub>1</sub> improved by 7.6% (p<0.0001) and 7.9% (p<0.0001) respectively at 18 weeks. VC improved by 10–20% in 8 patients and over 20% in 4 patients. FEV<sub>1</sub> improved by 10–20% in 5 patients and by over 20% in 7 patients. In the total study population with refractory sarcoidosis in their lungs or other organs (n=45), statistically significant improvements were seen in markers of disease activity and inflammation, lung function and health-related quality of life.

## Safety and tolerability

### Summary of product characteristics (Remicade)

In clinical trials of infliximab for the licensed indications, upper respiratory tract infection was the most common adverse drug reaction, occurring in 25.3% of infliximab-treated patients compared with 16.5% of control patients. Other very common adverse effects (occurring in 1 in 10 people or more) include viral infections (such as influenza and herpes virus infection), headache, sinusitis, abdominal pain, nausea, generalised pain and infusion-related reactions.

The most serious adverse drug reactions associated with the use of TNF-alpha inhibitors that have also been reported with infliximab include hepatitis B virus reactivation, congestive heart failure, serious infections (including sepsis, opportunistic infections and tuberculosis) and serious infusion reactions. Sarcoidosis and sarcoid-like reactions have been reported rarely. See the [summary of product characteristics](#) for a complete list.

Infliximab is contraindicated in people with tuberculosis or other severe infections, and people with moderate or severe heart failure (New York Heart Association; NYHA class III/IV). In 2014, the [Drug Safety Update](#) from the Medicines and Healthcare products Regulatory Agency (MHRA) advised that all patients should be assessed for active and latent tuberculosis before starting treatment with a TNF-alpha inhibitor.

Patients must be monitored closely for infections including tuberculosis before, during and 6 months after treatment with infliximab. Caution should be used when considering the use of infliximab in patients with chronic infection or in those with a history of recurrent infections, including concomitant immunosuppressive therapy. Caution is also advised in people with hepatitis B virus infection and mild heart failure.

## Randomised controlled trial

In the study by [Baughman et al. 2006](#), the proportions of patients who had adverse events were similar across the treatment groups. The most commonly reported adverse events (in more than 15% of patients in any group) were upper respiratory tract infection, coughing, dyspnoea and pain (sarcoidosis, bronchitis, headache and back pain). Infusion reactions were generally mild and occurred in similar proportions of infliximab- and placebo-treated patients. No cases of fungal infection, tuberculosis or opportunistic infections were reported.

At week 52, serious adverse events had occurred in 18.2% (8/44) of patients in the placebo group and 23.1% (21/91) of patients in the infliximab group. The most commonly reported serious adverse events (in more than 3% of patients in any group) were pneumonia, sarcoidosis and cardiac failure. Two patients taking placebo (4.5%) and 5 patients taking infliximab (5.5%) discontinued treatment due to adverse events. One person taking placebo died of respiratory failure caused by progression of sarcoidosis. One person taking infliximab 5 mg/kg died of epithelioid sarcoma after the study finished.

## Observational studies

In the prospective study by [Vorselaars et al. \(2015\)](#), 8/56 patients (14%) discontinued infliximab: 3 with pneumonia (1 of whom died), 1 with respiratory failure due to disease progression (who subsequently died), 1 with peritonitis (who was known to be on peritoneal dialysis), 1 with gastrointestinal problems, 1 with allergies and 1 who did not wish to continue for undisclosed reasons. Over 26 weeks, 13/56 patients (23%) had mild adverse effects including respiratory tract infections, headache, dizziness, oedema and joint pain. Thirty four patients had no adverse effects.

Over 46 months, in the retrospective study by [Russell et al. \(2013\)](#), adverse effects were seen in 15/26 patients (58%), 3 of whom discontinued infliximab treatment for severe pneumonia, a positive tuberculosis test and recurrent sinusitis. The most common adverse effects were minor infection (n=4), rash (n=4) and pneumonia (n=3).

[Van Rijswijk et al. \(2013\)](#) (n=45, duration 18 weeks) reported that few adverse effects were documented and the majority were mild. One patient was hospitalised with pneumonia. In the study by [Ørum et al. \(2012\)](#), 2 patients discontinued infliximab due to adverse effects (n=12, mean duration 25 months).

## Evidence strengths and limitations

The RCT by [Baughman et al. \(2006\)](#) found that infliximab improved the disease-oriented primary outcome (mean percent predicted FVC) at 24 weeks compared with placebo in people with stable pulmonary sarcoidosis. This is statistically significant; however, it is unclear whether the average improvement was clinically important. Also, there were no statistically significant differences in any of the major patient-oriented outcomes (such as health-related quality of life, dyspnoea or walking distance) at 24 weeks.

It is important to note that patients in the study had stable disease and were taking regular background corticosteroid and/or immunosuppressant therapy. Therefore, the results from this study may not reflect the effectiveness of infliximab in people with pulmonary sarcoidosis who have active, unstable disease for whom corticosteroids and other treatments have proven ineffective (or who cannot tolerate these treatments), in whom life expectancy may be reduced. It is possible that a small number of people in the study responded well to infliximab treatment, with little or no benefit seen in the majority, diluting the overall effect of infliximab observed in the study. Most people in the study had mildly impaired lung function and/or stage 2 or 3 pulmonary sarcoidosis but post hoc exploratory analyses suggested that patients with more severe sarcoidosis might benefit more from infliximab treatment than those with milder disease. However, these analyses have limitations and should be regarded as hypothesis-generating only. Further RCTs would be useful to answer this question but would be very difficult to perform because of the rarity of severe, refractory disease and issues around selecting an ethical comparator.

The uncontrolled [observational studies](#) in this evidence summary were undertaken in patients with refractory sarcoidosis. However, observational studies are more subject to [bias](#) and [confounding](#) than RCTs and interpretation of these studies is further limited by the absence of any form of comparator. The study by [Vorselaars et al. \(2015\)](#) was undertaken [prospectively](#) but was open-label. The other 3 studies were retrospective [case series](#). Limitations of these include differences in the management and follow-up of individual patients, inconsistent and incomplete recorded data, loss to follow-up and, potentially, missed patients. As is usual for a rare disease, the studies had small [sample sizes](#), particularly when considering the effects of infliximab on sarcoidosis in individual organs.

The studies are relevant to the overall UK population, although the study by [Russell et al. \(2013\)](#) mainly included people of African-American ethnicity. Sarcoidosis has been shown to be more severe and difficult to treat in this population, which is reflected in the lower

(non-significant) improvements in lung function seen in this study, compared with the other observational studies.

Disease-oriented outcomes were primarily used in the studies. [Van Rijswijk et al. \(2013\)](#) and [Vorselaars et al. \(2015\)](#) did find some statistically significant improvements in health-related quality of life in people with sarcoidosis in lung and other organs. However, these improvements did not always reach the level considered to be clinically important. Although improvements in FVC or VC and other lung function outcomes were seen in most of the studies, the minimal clinically important changes for sarcoidosis are unclear. Nevertheless, some patients seem to have seen substantial benefits and, in people with severe and active refractory disease, even stabilisation of lung function may be preferable to further deterioration.

The improvement in percent of predicted FVC seen in the studies in people with refractory sarcoidosis was generally higher than in the RCT by [Baughman et al. \(2006\)](#) in people with stable sarcoidosis (around 7%, compared with 2.5%). This may be because people with refractory sarcoidosis experience more inflammation, which may respond to infliximab. However, more studies are needed to confirm this.

From the studies included in the evidence review, the optimal dose, administration regimen and duration of infliximab treatment is unclear. Also, it is not known whether any benefits obtained in the short term will be maintained long term.

The evidence supports [BTS guidance](#) that immunosuppressants such as infliximab have only a limited role in pulmonary sarcoidosis because there are insufficient high-quality studies to confirm their place in therapy and they have significant adverse effects. Immunosuppressants should be used only when disease is refractory to standard treatments and when there are no pharmacological alternatives.

## Context and estimated impact for the NHS

### Cost effectiveness

No studies were identified on the cost effectiveness of infliximab for treating any manifestation of sarcoidosis.

According to [MIMS](#) (October 2016), 1 vial of infliximab 100 mg powder for concentrate for

solution for infusion costs £419.62 for Remicade, £377.66 for Inflectra or Remsima and £377.00 for Flixabi (excluding VAT).

The table below shows the cost of infliximab treatment based on the doses of infliximab and treatment regimens used in the RCT by [Baughman et al. \(2006\)](#). However, these costs are for the medicine only (excluding VAT) and do not include any local procurement discounts or other costs incurred, such as dilution and administration, or standard supportive therapy. They also assume that vials are used for only 1 patient and are not shared between patients.

**Table 3 Cost of a course of infliximab treatment**

Infliximab dose <sup>a</sup>	Administration regimen	Cost of Flixabi <sup>b</sup>	Cost of Inflectra or Remsima <sup>b</sup>	Cost of Remicade
3 mg/kg, 240 mg	Weeks 0, 2, 6, 12, 18 and 24	£6,786.00	£6,797.88	£7,553.16
5 mg/kg, 400 mg		£9,048.00	£9,063.84	£10,070.88

<sup>a</sup> Based on treating an 80 kg person.

<sup>b</sup> For more information on biosimilar medicines see the [NICE Key therapeutic topic on biosimilar medicines](#), which provides links to other resources including [answers to commonly asked questions about biosimilar versions of infliximab](#).

## Current drug usage

No information on the use of infliximab for any manifestation of sarcoidosis in UK clinical practice was identified 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 sarcoidosis who are thinking about trying infliximab.

## Relevance to NICE guidance programmes

NICE has not published any guidance on managing sarcoidosis. The use of infliximab for sarcoidosis is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other NICE work programme.

NICE has published guidance on many of the licensed indications for infliximab. Please see the [NICE website](#) for more information.

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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 Colm Leonard has been an investigator in trials of new drugs in idiopathic pulmonary fibrosis involving the following companies; Roche; Boehringer Ingelheim; InterMune; AstraZeneca and Actelion. He does not accept honoraria from these companies but his department has gained funding from clinical trial work and he has attended conferences paid for by these companies.

Professor Athol U Wells declared no relevant interests.

### **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.**

ISBN: 978-1-4731-2224-6