

Refractory extrapulmonary sarcoidosis: infliximab

Evidence summary

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www.nice.org.uk/guidance/es4

Key points from the evidence

The content of this evidence summary was up-to-date in January 2017. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

Because no randomised controlled trials were identified, this evidence summary includes 10 observational studies that assessed the effects of infliximab for treating active, unstable extrapulmonary sarcoidosis in people who had found corticosteroids and other immunosuppressants to be ineffective, or who could not tolerate these treatments (refractory sarcoidosis).

The studies included 155 cases of refractory extrapulmonary sarcoidosis, primarily in the nervous system (34%) or skin (25%), who were treated with infliximab. Of these cases, extrapulmonary sarcoidosis resolved in a third and improved in around half. However,

observational studies are subject to bias and confounding and have many limitations affecting their application to clinical practice.

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

According to specialists involved in this evidence summary, infliximab may be an option for some patients with severe, refractory extrapulmonary sarcoidosis (particularly cutaneous or neurological sarcoidosis); for example, those affected by disabling or disfiguring disease, or whose life expectancy is likely to be reduced.

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"> • Of 155 cases of refractory extrapulmonary sarcoidosis treated with infliximab in 1 prospective open-label study (Vorselaars et al. 2015) and 9 retrospective case reviews (Aguiar et al. 2011, Chapelon-Abric et al. 2015, Doty et al. 2005, Hostettler et al. 2011, Ørum et al. 2012, Panselinas et al. 2009, Russell et al. 2013, Sweiss et al. 2005 and Van Rijswijk et al. 2013): <ul style="list-style-type: none"> – the disease resolved in 51 (33%), improved in 71 (46%), resolved or improved in 10 (with individual data for each outcome not reported, 6%), remained stable in 22 (14%) and deteriorated in 1 (1%). – neurological sarcoidosis (n=52) resolved in 21 (40%) improved in 24 (46%) and remained stable in 7 (13%). – cutaneous sarcoidosis (n=38) resolved in 14 (37%), improved in 19 (50%), resolved or improved in 4 (with individual data for each outcome not reported, 11%) and remained stable in 1 (3%). 	<ul style="list-style-type: none"> • 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 Remicade summary of product characteristics for a complete list. • Adverse events seen in the studies reflected those listed in the summary of product characteristics (for example respiratory tract infections including pneumonia, headache, joint pain, oedema and rashes).

<ul style="list-style-type: none"> The studies did not have control arms; therefore, it is unclear what proportions of patients would have seen an improvement, stabilisation or deterioration in sarcoidosis without infliximab treatment. 	
<p>Patient factors</p> <ul style="list-style-type: none"> Across the studies, about 15% of patients discontinued treatment due to adverse events. Patients should be tested for hepatitis B virus and active and latent tuberculosis before starting treatment (Remicade summary of product characteristics). Patients must be monitored closely for infections including tuberculosis before, during and 6 months after treatment with infliximab (Remicade summary of product characteristics). The studies were undertaken in people with active, unstable sarcoidosis that was refractory to standard treatments. Results suggest that infliximab may be an option for some of these patients, but they cannot be generalised to people with stable disease or those who have not tried standard treatments. 	<p>Resource implications</p> <ul style="list-style-type: none"> A 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 (MIMS, November 2016). A 12-month course of infliximab costs about £11,000 to £17,000 for an 80 kg person depending on the product and dosage used. 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. 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.

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. 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 (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 usually recommended first-line. Other treatments that may be added if the disease does not respond, or if a steroid-sparing agent is needed, include methotrexate, hydroxychloroquine, leflunomide and infliximab (Sarcoidosis, [Oxford Textbook of Medicine](#)).

This evidence summary considers the best available evidence for infliximab for treating common manifestations of chronic, refractory extrapulmonary sarcoidosis. A related evidence summary has considered infliximab for [pulmonary 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 is based on the best available evidence for infliximab for treating chronic, refractory extrapulmonary sarcoidosis in any organ. Because no randomised controlled trials were identified, it includes 10 observational studies that were undertaken in people with active, unstable sarcoidosis (pulmonary or extrapulmonary) for whom corticosteroids and other immunosuppressants had proven ineffective, or who could not tolerate these treatments (refractory sarcoidosis). Studies which looked at individual manifestations of sarcoidosis were not included, nor were studies in stable sarcoidosis.
- The 10 included studies are a prospective study by [Vorselaars et al. \(2015\)](#) (n=56, main indication extrapulmonary sarcoidosis in 22 patients) and 9 retrospective case reviews by [Aguilar et al. \(2011\)](#) (n=10, main indication extrapulmonary sarcoidosis in 9 patients), [Chapelon-Abric et al. \(2015\)](#) (n=16, including 21 extrapulmonary sarcoidosis indications), [Doty et al. \(2005\)](#) (n=10, main indication extrapulmonary sarcoidosis in all 10 patients), [Hostettler et al. \(2011\)](#) (n=16, main indication extrapulmonary sarcoidosis in 11 patients), [Ørum et al. \(2012\)](#) (n=12, including 9 extrapulmonary sarcoidosis indications), [Panselinas et al. \(2009\)](#) (n=14, main indication extrapulmonary sarcoidosis in 13 patients), [Russell et al. \(2013\)](#) (n=26, including 38 extrapulmonary sarcoidosis indications), [Sweiss et al. \(2005\)](#) (n=9, main indication extrapulmonary sarcoidosis in all 9 patients) and [Van Rijswijk et al. \(2013\)](#) (n=45, main indication extrapulmonary sarcoidosis in 22 patients).

- Eight of the studies (1 prospective study and 7 retrospective case reviews) reported 52 cases of refractory **neurological** sarcoidosis treated with infliximab, including 23 with sarcoidosis in the brain and central nervous system. Of these 21 (40%) experienced complete remission, 24 (46%) experienced partial remission and 7 (13%) experienced no change in the disease.
- Outcomes for 38 cases of refractory **cutaneous** sarcoidosis treated with infliximab, including 13 reported to be lupus pernio (lesions on the face), were included in 9 of the studies (1 prospective study and 8 retrospective case reviews). Lesions resolved in 14 (37%), improved in 19 (50%), resolved or improved in 4 (with individual data for each outcome not reported, 11%) and remained stable in 1 (3%).
- Thirteen patients with various manifestations of refractory **ocular** sarcoidosis were reported in 7 retrospective case reviews. Ocular sarcoidosis resolved with infliximab treatment in 3 patients (23%) and improved in 8 patients (62%); no change was seen in 2 patients (15%).
- Refractory **lymph node** sarcoidosis was reported for 14 patients who received infliximab in 4 retrospective case reviews. Of these, the disease resolved or improved in 6 (43%), was unchanged in 7 (50%) and deteriorated in 1 (7%).
- Across 5 retrospective case reviews of infliximab for refractory sarcoidosis, 4 patients had the disease in **bones** (1 in the bone marrow), 3 patients had it in **muscles** and 2 patients had it in **joints**. The sarcoidosis resolved with treatment in 3 patients (33%), improved in 5 patients (56%) and remained unchanged in 1 patient (11%). One patient who initially saw improvements subsequently worsened.
- Seven patients in 3 retrospective case series received infliximab for refractory **cardiac** sarcoidosis. Of these 4 (57%) experienced complete remission of the disease and 3 (43%) experienced partial remission.
- Refractory sarcoidosis in the **upper respiratory tract** was treated with infliximab in 6 patients reported in 4 retrospective case reviews. It resolved in 3 patients (50%), improved in 1 patient (17%) and remained unchanged in 2 patients (33%).
- Across 5 of the retrospective case reviews in the evidence summary, 2 patients had sarcoidosis in the **spleen** and 4 patients had sarcoidosis in the **liver**. The disease resolved with infliximab treatment in 2 patients (33%), improved in 2 patients (33%) and was unchanged in 2 patients (33%).

- Of 2 patients, **kidney** sarcoidosis resolved in 1 and improved in the other. One patient with **oesophageal** sarcoidosis and 7 patients with **severe fatigue** also saw improvements in the disease.
- Across the studies, about 15% of patients discontinued treatment due to adverse events. 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.
- [Observational studies](#) are subject to [bias](#) and [confounding](#) and have many limitations affecting their application to clinical practice. The study by [Vorselaars et al. \(2015\)](#) was undertaken [prospectively](#) but was open-label. The other 9 studies were retrospective [case series](#), which were generally undertaken in single centres. Other limitations of case series include differences in the management and follow-up of individual patients, inconsistent and incomplete recorded data, loss to follow-up and, potentially, missed patients. All of the studies in the evidence summary were uncontrolled and, as is usual for rare diseases, had small [sample](#) sizes, particularly when considering the effects of infliximab on sarcoidosis in individual organs. Many of the outcomes assessed were surrogate or disease-oriented outcomes, rather than patient-oriented outcomes, and the level of response was often determined by a single specialist clinician only. Definitions of response to treatment were often not reported and may have varied across the studies. Nevertheless, some patients seem to have seen substantial benefits and, in people with severe and active refractory disease, even stabilisation of the condition may be preferable to further deterioration.
- According to specialists involved in this evidence summary, infliximab may be an option for some patients with severe, refractory extrapulmonary sarcoidosis (particularly cutaneous or neurological sarcoidosis); for example, those affected by disabling or disfiguring disease, or whose life expectancy is likely to be reduced.

[Full text of evidence review.](#)

Context and estimated impact for the NHS

According to [MIMS](#) (November 2016), a 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 12-month course of infliximab treatment is about £11,000 to £17,000 for an 80 kg person depending on the product and dosage used (generally 3 mg/kg or 5 mg/kg at weeks 0, 2 and 6, then 6-weekly). 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.

[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 (see the evidence summary on [pulmonary sarcoidosis](#) for more information). The skin is the second most commonly affected organ. Manifestations include hyperpigmentation, hypopigmentation, keloid reaction, lupus pernio (lesions on the face) and erythema nodosum (red nodules, commonly on the shins). Other organs such as the eyes, brain, nervous system, liver and heart may also be affected (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 and, in some cases, the disease will become chronic and persist for more than 5 years. 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](#)).

The natural course of sarcoidosis is difficult to predict and there are significant differences in the severity of disease and the organs involved depending on the ethnicity of the person. Treatment is not recommended for everyone because of the high rate of spontaneous remission and the risk of adverse effects. The treatment decision is usually based on symptoms, the extent of symptomatic disease, whether the sarcoidosis is acute or chronic, and the risk of life-threatening complications. First-line treatment is usually with corticosteroids such as prednisolone. Topical corticosteroid creams and eye drops may be effective if inflammation is superficial. Other treatments that may be added if the disease does not respond, or if a steroid-sparing agent is needed, include methotrexate, hydroxychloroquine, leflunomide and infliximab (Sarcoidosis, [Oxford Textbook of](#)

[Medicine](#)).

This evidence summary considers the best available evidence for infliximab for treating common manifestations of chronic, refractory extrapulmonary sarcoidosis. A related evidence summary has considered [infliximab for pulmonary 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 of 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](#) (November 2016), a 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 take into account 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 chronic, refractory extrapulmonary sarcoidosis in any organ. Because no randomised controlled trials were identified, it includes 10 observational studies (1 [prospective study](#) and 9 [case series](#)) that considered use of infliximab in people with various manifestations of sarcoidosis. Studies which looked at individual manifestations of sarcoidosis were not included, nor were studies in stable sarcoidosis.

Table 1 Summary of study backgrounds

Study design	Patients	Interventions	Key outcomes
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<p><u>Vorselaars et al. 2015</u> Prospective, uncontrolled open-label study in the Netherlands</p>	<p>56 patients (mean age 48 years, 87.5% white) with severe^a sarcoidosis (mean duration 6.8 years) unresponsive to first- and second-line treatment^b (n=52) or who had had severe adverse effects from treatments^{c, d}.</p> <p>Main sarcoidosis treatment indication:</p> <ul style="list-style-type: none"> • 11 neurological (8 peripheral, 3 CNS) • 4 cutaneous • 2 cardiac • 34 pulmonary. <p>5 patients had other, less common types of extrapulmonary disease (sinus, myositis, vocal cord paralysis, ossal and hypercalcaemia).</p>	<p>Infliximab 5 mg/kg at weeks 0 and 2 then every 4 weeks for 6 months (8 infusions).</p>	<p>Response to treatment (for example, using photographs for cutaneous sarcoidosis and clinical judgement for neurological sarcoidosis). Quality of life (PGA and SF-36 scores). Adverse effects.</p>
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<p><u>Aguiar et al. 2011</u> Retrospective case review in Portugal</p>	<p>10 patients (mean age 47 years, 100% white) with sarcoidosis resistant to corticosteroid or alternative treatments, or with unacceptable adverse effects with these treatments^e.</p> <p>Main sarcoidosis treatment indication:</p> <ul style="list-style-type: none"> • 3 neurological • 3 cutaneous (1 lupus pernio) • 1 each splenomegaly, hepatic cirrhosis, lachrymal gland and pulmonary. 	<p>Infliximab 5 mg/kg at weeks 0 and 2 then every 8 weeks for 1 year (all patients had at least 7 infusions).</p>	<p>None prespecified. Efficacy and adverse effects described for individual patients.</p>
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<p><u>Chapelon-Abric et al. 2015</u> Retrospective case review in France</p>	<p>16 patients (median age 36 years, mixed ethnicities) with chronic^f (median duration 91 months), severe^g sarcoidosis refractory to treatment with a corticosteroid and 1 (n=4) or more immunosuppressant (n=12).</p> <p>Sarcoidosis indication for infliximab treatment (some patients needed treatment for more than 1 organ):</p> <ul style="list-style-type: none"> • 12 neurological • 4 cardiac • 3 pulmonary. <p>Cutaneous, ocular, lymph node, liver and joint sarcoidosis were each seen in 1 person.</p>	<p>Infliximab 3 mg/kg (5 patients) or 5 mg/kg (11 patients) initially at weeks 0, 2 and 6 then every 8 weeks (median 15 infusions).</p> <p>If response was suboptimal, the dosage was increased to 7.5 mg/kg and/or the treatment interval was reduced to 6 or 4 weeks.</p>	<p>Efficacy (complete or partial response or treatment failure^h).</p> <p>Change in dosage of corticosteroid and other treatments.</p> <p>Adverse effects.</p>
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<p><u>Doty et al. 2005</u> Retrospective case review in the USA</p>	<p>10 patients (mean age 37 years, ethnicity not reported) with sarcoidosis (mean duration 9.2 years) refractory to other treatments (n=9), or in whom other treatments were poorly tolerated because of adverse effects (n=4, 3 of whom also experienced treatment failure).</p> <p>Main sarcoidosis indication for infliximab treatment:</p> <ul style="list-style-type: none"> • 5 lupus pernio (1 plus upper respiratory tract) • 1 each of cutaneous (non-lupus pernio) plus ocular, bone, liver, CNS and muscle. 	<p>Infliximab 5 mg/kg at weeks 0, 2 and 6 then generally every 8 weeks (treatment duration 3 to 20 doses).</p>	<p>Objective efficacy assessments (such as photographs, clinical examinations, blood tests and imaging). Improvement in symptoms. Change in corticosteroid dosage.</p>
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<p><u>Hostettler et al. 2011</u> Retrospective case review in Switzerland</p>	<p>16 patients (mean age 51 years, 100% white) with chronic progressive sarcoidosis (mean duration 12 years) who either had steroid-resistant disease, were refractory to steroid-sparing treatment, or developed severe adverse effects with treatmentsⁱ.</p> <p>Main sarcoidosis treatment indication:</p> <ul style="list-style-type: none"> • 6 CNS • 5 pulmonary • 4 lupus pernio • 1 cardiac. <p>The other 12 patients (5 pulmonary and 7 extrapulmonary sarcoidosis) were started on infliximab but received less than 12 months' treatment.</p>	<p>Typically infliximab 3 mg/kg at 4- to 6-weekly intervals for at least 12 months (mean duration 29 months).</p>	<p>Treatment response (complete remission, partial remission or no response [not defined]) assessed by specialist clinicians.</p> <p>Adverse effects.</p>
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<p><u>Ørum et al. 2012</u> Retrospective case review in Denmark</p>	<p>12 patients (mean age 34 years at diagnosis, 92% white) with sarcoidosis (mean duration 5.8 years) refractory to standard immunotherapy (n=2) or with intolerable adverse effects on standard therapy (n=2) or both (n=8).</p> <p>Sarcoidosis treatment indication (some patients were affected in more than 1 organ):</p> <ul style="list-style-type: none"> • 9 pulmonary • 2 cutaneous • 2 ocular • 1 each of oesophagus, bone marrow, kidney, lymph nodes and nose. 	<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).</p>	<p>Clinical observations and specific examinations. Patient-experienced improvements. Adverse effects.</p>
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<p><u>Panselinas et al. 2009</u> Retrospective case review in the USA</p>	<p>14 patients (mean age 43 years, 71% African-American) with sarcoidosis (mean duration 4.7 years) refractory to standard treatments (n=9) or with adverse effects on standard treatment (n=4) who had discontinued infliximab for at least 8 weeks. The reason for initiating infliximab was unknown for 1 person.</p> <p>Main sarcoidosis treatment indication:</p> <ul style="list-style-type: none"> • 5 CNS • 4 cutaneous (3 lupus pernio) • 1 each of muscle, vertebral spine, joint, pulmonary, upper respiratory tract. 	<p>Infliximab 5 mg/kg at weeks 0, 2 and 6 then every 6 weeks (treatment duration ranged from 1 dose to 10.5 months).</p>	<p>Sarcoidosis in the index organ was classified as 'resolved', 'improved', 'stable' or 'deteriorated' using objective measures (such as radiography). Subjective physical and psychosocial limitations described by patients. Changes in corticosteroid dosage.</p>
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<p><u>Russell et al. 2013</u> Retrospective case review in the USA</p>	<p>26 patients (mean age 51 years, 81% African-American) with sarcoidosis (average duration 14.9 years) refractory to corticosteroids or DMARDs or both, or who could not tolerate these treatments. Previous ineffective treatments included corticosteroids (n=24), methotrexate (n=20) and hydroxychloroquine (n=23).</p> <p>Sarcoidosis treatment indication (some patients were affected in more than 1 organ):</p> <ul style="list-style-type: none"> • 15 pulmonary • 11 cutaneous • 11 lymph node • 8 CNS • 3 ocular • 1 each of liver, kidney, sinus, bone and muscle. 	<p>The average maximum infliximab dose was 511 mg (range 300 to 1,000 mg) given on average every 5.5 weeks (range 4–6 weeks, average treatment duration 46.2 months).</p>	<p>Objective data (such as imaging, laboratory tests or clinician assessment) was used to grade clinical response as 'resolved', 'improved', 'unchanged' or 'progressed'[†].</p> <p>The same scale was used for patient-reported symptom response to treatment.</p> <p>Adverse effects.</p>
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<p><u>Sweiss et al. 2005</u> Retrospective case review in the USA</p>	<p>9 patients (mean age 53 years, 89% African-American) with sarcoidosis (duration 6 months to 13 years) who had been treated with oral corticosteroids (n=3) and/or corticosteroid-sparing treatments (n=6), without significant response or with adverse effects requiring discontinuation of treatment.</p> <p>Main sarcoidosis treatment indication:</p> <ul style="list-style-type: none"> • 3 upper respiratory tract • 3 cutaneous • 1 each of lymphadenopathy, splenomegaly and profound fatigue, and conjunctivitis. 	<p>Infliximab 3–5 mg/kg at weeks 0, 2 and 6, then every 6–8 weeks based on clinical response.</p>	<p>Response to therapy (not defined). Adverse effects.</p>
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<p><u>Van Rijswijk et al. 2013</u> Retrospective case review in the Netherlands</p>	<p>45 patients (mean age 49 years, race not reported) with sarcoidosis (mean duration 7.6 years) refractory to regular medication or who had severe adverse effects with these medicinesⁱ. Main sarcoidosis treatment indication:</p> <ul style="list-style-type: none"> • 23 pulmonary • 9 neurological • 7 extreme fatigue • 4 uveitis • 2 cardiac. 	<p>Infliximab 5 mg/kg at weeks 0, 2, 6, 10, 14 and 18.</p>	<p>Markers of disease activity (such as F-FDG PET and serum markers). Health-related quality of life (CIS and SF-36). Adverse effects.</p>
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Abbreviations: CIS, Checklist Individual Strength, a generic fatigue questionnaire (range 8–56 with higher scores indicated more fatigue); CNS, central nervous system; DMARD, disease-modifying anti-rheumatic drug; F-FDG PET, ¹⁸F-fluorodeoxyglucose by positron emission tomography; PGA, patient global assessment, a measure of health-related quality of life (range 0–100 with higher scores indicating worse health); SF-36, 36-item Short Form health survey (range 0 to 100 with lower scores indicating a worse level of functioning); TNF tumour necrosis factor.

^a 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.

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

^c For example, worsening diabetes, psychological deterioration or liver function disorders.

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

^e For example, diabetes, depressive syndrome, psychotic behaviour, arterial hypertension or osteoporosis.

^f Still active 18 months after diagnosis.

^g Severity of sarcoidosis in the primary organ being treated with infliximab was assessed using a 7-point scoring system ranging from 0–6 with higher scores indicating more severe disease.

^h Complete response was defined as the absence of functional signs and a normalisation of imaging. Partial response was defined as the persistence of physical signs and/or abnormal imaging. Therapeutic failure was defined as the absence of clinical and/or laboratory improvement.

ⁱ Individual numbers of patients with treatment failure or adverse events were not reported.

^j Resolved was defined as complete resolution of clinical disease activity. Improved was defined as reduced sarcoid burden or reduced frequency in disease activity but still evidence of disease. Unchanged was defined as disease activity that was no different from before infliximab treatment. Progressed was defined as the presence of clinical features of progressive disease despite infliximab treatment.

Table 2 Summary of study results

Study design	Efficacy	Adverse events
<p data-bbox="137 371 384 450"><u>Vorselaars et al. 2015</u></p> <p data-bbox="137 477 421 891">Prospective, uncontrolled open-label study in the Netherlands (n=56, main indication extrapulmonary sarcoidosis in 22 patients).</p>	<p data-bbox="443 371 919 450">After 26 weeks' treatment with infliximab:</p> <ul data-bbox="459 501 1050 902" style="list-style-type: none"> <li data-bbox="459 501 1050 730">• All 4 patients with cutaneous sarcoidosis had marked improvement or total resolution of skin lesions confirmed by photograph and clinical comparison. <li data-bbox="459 770 1050 902">• All 8 patients with peripheral neuropathy had improvement of symptoms. <p data-bbox="443 947 959 1077">Results for other individual manifestations of extrapulmonary sarcoidosis were not reported.</p> <p data-bbox="443 1104 1046 1424">At 26 weeks in the total population (n=56), measures of health-related quality of life improved by a statistically significant amount (mean PGA -14.6 from baseline of 61.0, $p < 0.0001$; mean SF-36 [physical functioning] +8.2 from baseline of 40.6, $p = 0.009$).</p> <p data-bbox="443 1451 1007 1671">At 26 weeks in 19 patients taking prednisolone, the mean daily dose decreased by 8.8 mg ($p = 0.001$). No patients increased their concomitant immunosuppressant dose.</p>	<p data-bbox="1070 371 1430 880">In the total study population, 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>

<p><u>Aguiar et al. 2011</u> Retrospective case review in Portugal (n=10, main indication extrapulmonary sarcoidosis in 9 patients).</p>	<p>Of 3 patients with neurological sarcoidosis who received infliximab, 1 had complete resolution of CNS lesions, another had resolution of brain lesions and visual acuity became normal, and 1 saw no improvement in neurological symptoms and discontinued infliximab.</p> <p>In 1 person with lupus pernio, skin lesions improved significantly with infliximab and disease became stable, without the need for further treatment. Cutaneous plaques and 95% of cutaneous nodules disappeared in 1 person, and another had a 50% reduction in cutaneous nodules and experienced reduced pain from these.</p> <p>A person with splenomegaly had subjective improvement with infliximab but this could not be quantified, and a person with hepatic cirrhosis continued to have abnormal laboratory test results. In a person with chronic obstruction of both lachrymal glands, infliximab resolved symptoms.</p> <p>Corticosteroids or other treatments were stopped in 4 patients, the dosage was reduced in 3 patients and corticosteroids were added to infliximab in 1 patient.</p>	<p>2 people did not complete a year of treatment, 1 due to lack of response, and the second due to non-infectious pneumonia. No other significant adverse effects were seen.</p>
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<p><u>Chapelon-Abric et al. 2015</u></p> <p>Retrospective case review in France (n=16, including 21 extrapulmonary sarcoidosis indications).</p>	<p>After a median 57 months, complete remission^a of cardiac and CNS sarcoidosis was seen with infliximab in 4/4 and 11/12 cases respectively. Remission was also seen in people with other manifestations of sarcoidosis (cutaneous, ocular, lymph node, liver and joint). No response was seen in the other person with neurological sarcoidosis.</p> <p>Overall, of 16 patients, partial remission was seen in 9 and complete remission was seen in 6. Severity scores^b improved by a statistically significant amount following infliximab (median 6 at baseline compared with 2 at follow-up, p<0.001). The median dosage of corticosteroid at baseline was 15 mg compared with 8.5 mg after infliximab, but the difference did not reach statistical significance.</p> <p>Infliximab treatment was continued in 5/16 people. 3/11 patients who stopped infliximab relapsed.</p>	<p>After a median of 6 infusions, 10/16 patients discontinued infliximab: 7 due to infection, 1 due to paradoxical sarcoidosis, 1 due to leucoencephalopathy and 1 due to personal choice.</p>
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<p><u>Doty et al. 2005</u> Retrospective case review in the USA (n=10, main indication extrapulmonary sarcoidosis in all 10 patients).</p>	<p>Of 5 patients with disfiguring lupus pernio who received infliximab, the rash resolved in 1 and improved in the other 4. Upper respiratory tract symptoms (particularly hoarseness) also improved in 1 of these patients. Rash and eye pain improved in a patient with cutaneous (non-lupus pernio) and ocular sarcoidosis (uveitis). Improved fatigue, pruritus and pain were experienced by a patient with liver sarcoidosis, and hepatomegaly and jaundice resolved. A patient with CNS sarcoidosis experienced resolution of headaches, paraesthesias and seizure frequency.</p> <p>Pain and swelling improved in a patient with myositis, although worsening was subsequently seen on MRI. A patient with sarcoidosis in the spine saw no improvement in symptoms with infliximab but the lesion was less conspicuous on MRI after treatment.</p> <p>6 patients were receiving corticosteroids before infliximab therapy, and the dose was successfully reduced in 5 after therapy.</p>	<p>1 patient experienced anaphylaxis with infliximab after taking it for over a year. Another developed angioimmunoblastic lymphoma, although a causal relationship with infliximab was not established. A patient who was also taking inhaled beclometasone developed oral candidiasis.</p>
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<p><u>Hostettler et al. 2011</u> Retrospective case review in Switzerland (n=16, main indication extrapulmonary sarcoidosis in 11 patients).</p>	<p>Of 6 patients with CNS sarcoidosis, 3 experienced complete remission, 2 experienced partial remission and 1 experienced no response to infliximab treatment (definitions of response were not reported). 3 patients with lupus pernio experienced complete remission and 1 experienced partial remission. 1 patient with cardiac sarcoidosis experienced partial remission.</p>	<p>15/16 patients had no clinically relevant adverse effects with infliximab over a mean of 29 months. After tolerating treatment for 4 years, 1 patient had bradycardia 6 hours after an infliximab infusion. The patient received a pacemaker and infliximab was restarted without recurrence of cardiac symptoms.</p>
<p><u>Ørum et al. 2012</u> Retrospective case review in Denmark (n=12, including 9 extrapulmonary sarcoidosis indications).</p>	<p>In 2 patients with ocular sarcoidosis (uveitis and cystoid macular oedema), infliximab controlled ocular inflammation without the need for corticosteroids. Cutaneous sarcoidosis resolved with infliximab treatment in 2 patients. Patients with sarcoidosis in other organs (oesophagus, bone marrow, kidney, nose and lymph nodes) all reported subjective improvement in symptoms.</p>	<p>2 patients discontinued infliximab due to adverse effects.</p>

<p><u>Panselinas et al. 2009</u> Retrospective case review in the USA (n=14, main indication extrapulmonary sarcoidosis in 13 patients).</p>	<p>CNS sarcoidosis resolved with infliximab treatment in 1 patient, with brain MRI appearing normal. 3 patients experienced improvement in CNS sarcoidosis (mental status and brain MRI improved and diabetes insipidus resolved in the first, tremors decreased in the second, and mental status and hydrocephalus improved in the third). Another patient with visual defects caused by CNS sarcoidosis remained stable, although this patient only received 1 dose of infliximab.</p> <p>Of 3 patients with lupus pernio, rash improved in 2 and remained stable in the other. Rash resolved in a further patient with cutaneous sarcoidosis.</p> <p>Pain, oedema, induration and MRI findings improved in a patient with muscle sarcoidosis. Improvements on MRI were also seen in a patient with sarcoidosis in the spine. Arthritis remained stable in a patient with sarcoidosis in their joints, and hoarseness, dysphagia and dyspnoea remained stable in a patient with sarcoidosis in the upper respiratory tract.</p> <p>The dose of corticosteroid was reduced in 6/12 patients while they had infliximab but 3/12 needed a dose increase.</p> <p>Patients who discontinued infliximab were followed for a mean of 12 months. At the end of the follow-up period, 12/14 patients deteriorated (half within 3 months of stopping infliximab) and 2/</p>	<p>Adverse events were not reported.</p>
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	14 remained stable (1 with pulmonary sarcoidosis and 1 with lupus pernio, both which were stable with infliximab).	
<u>Russell et al. 2013</u> Retrospective case review in the USA (n=26, including 38 extrapulmonary sarcoidosis indications).	<p>Of 11 patients with cutaneous sarcoidosis treated with infliximab, when objective clinical outcomes were considered, disease resolution^c was seen in 4 and sustained improvement was seen in 7 (p=0.005^d).</p> <p>Of 8 patients with CNS sarcoidosis, clinical resolution was seen in 3, sustained clinical improvement in disease activity was seen in 2 and no change was seen in 3 (p=0.03).</p> <p>According to clinical evidence, lymph node sarcoidosis was unchanged in 7/11 patients who received infliximab, progressed in 1/11, and resolved or improved in 3/11 (no significant difference).</p> <p>Of 3 patients with ocular sarcoidosis, 1 experienced resolution of the disease and 2 experienced no change. Single cases of kidney, bone and muscle sarcoidosis resolved with treatment. In contrast, cases of liver and sinus disease remained unchanged.</p>	<p>Over 46.2 months, adverse effects were seen in 15/26 patients, 3 of whom discontinued infliximab (due to severe pneumonia, positive tuberculosis skin test and recurrent sinusitis).</p> <p>Minor infection, rash and pneumonia were the most commonly reported adverse effects (n=4, n=4 and n=3 respectively).</p>

<p><u>Sweiss et al. 2005</u> Retrospective case review in the USA (n=9, main indication extrapulmonary sarcoidosis in all 9 patients).</p>	<p>In 3 patients with sarcoidosis in the upper respiratory tract who had infliximab, signs and symptoms of nasal obstruction and sinusitis resolved completely.</p> <p>Of 3 patients with cutaneous sarcoidosis, lesions resolved completely in 2 and partially resolved in the other.</p> <p>In a patient with lymphadenopathy, lymph nodes in the neck resolved but those in the chest and abdomen only partially regressed. Splenomegaly resolved completely in 1 patient, and necrotising conjunctivitis and vision improved by 90% in another.</p> <p>Patients experienced no recurrence of symptoms during the follow-up period of 4–42 months.</p>	<p>Infliximab was discontinued in 1 patient due to drug-induced lupus, which resolved after treatment was stopped. The other 8 patients experienced no major adverse effects.</p>
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<p><u>Van Rijswijk et al. 2013</u> Retrospective case review in the Netherlands (n=45, main indication extrapulmonary sarcoidosis in 22 patients).</p>	<p>After receiving infliximab, 2 patients with cardiac sarcoidosis experienced an improvement in left ventricular ejection fraction (from 37% to 60% and 35% to 45–50% respectively) and symptoms such as arrhythmias, palpitations, dizziness and/or dyspnoea on exertion.</p> <p>Vision improved in 4 patients with severe uveitis measured objectively. 9 patients with neurological complications and 7 patients with severe fatigue showed improvement in fatigue severity and quality of life scores, although details are not reported.</p> <p>In the total study population, statistically significant improvements were seen in fatigue severity scores (–5.3 points on CIS, p=0.003) and physical functioning scores(+12.6 points on SF-36, p=0.011).</p>	<p>Infliximab was generally well-tolerated. 1 patient was hospitalised because of pneumonia.</p>
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Abbreviations: CIS, Checklist Individual Strength, a generic fatigue questionnaire (range 8–56 with higher scores indicated more fatigue); CNS, central nervous system; p, p value; PGA, patient global assessment, a measure of health-related quality of life (range 0–100 with higher scores indicating worse health); SF-36, 36-item Short Form health survey (range 0 to 100 with lower scores indicating a worse level of functioning).

^a Complete response was defined as the absence of functional signs and a normalisation of imaging. Partial response was defined as the persistence of physical signs and/or abnormal imaging. Therapeutic failure was defined as the absence of clinical and/or laboratory improvement.

^b Severity of sarcoidosis in the primary organ being treated with infliximab was assessed using a 7-point scoring system ranging from 0–6, with higher scores indicating more severe disease.

^c Resolved was defined as complete resolution of clinical disease activity. Improved was defined as reduced sarcoid burden or reduced frequency of disease activity but still evidence of disease. Unchanged was defined as disease activity that was no different from before infliximab treatment. Progressed was defined as the presence of clinical features of progressive disease despite infliximab treatment.

^d A statistical tool was used to compare the number of patients whose sarcoidosis resolved or improved with those whose disease was unchanged or deteriorated.

Clinical effectiveness

Neurological sarcoidosis

Eight of the studies (1 prospective study and 7 retrospective case reviews) in this evidence summary reported 52 cases of refractory neurological sarcoidosis treated with infliximab, including 23 with sarcoidosis in the brain and central nervous system (CNS). Of these 21 (40%) experienced complete remission, 24 (46%) experienced partial remission and 7 (13%) experienced no change in the disease.

In Aguilar et al. (2011), 1 patient with neurological sarcoidosis who received infliximab had complete resolution of CNS lesions and another had resolution of brain lesions and visual acuity became normal. A patient with CNS sarcoidosis in Doty et al. (2005) experienced resolution of headaches, paraesthesias and seizure frequency. Complete remission of CNS sarcoidosis was also seen in 11 patients in Chapelon-Abric et al. (2015), 3 patients in

Hostettler et al. (2011), 1 patient in Panselinas et al. (2009) and 3 patients in Russell et al. (2013).

In the prospective study by Vorselaars et al. (2015), 8 patients with peripheral neuropathy had improvement of symptoms with infliximab. Two patients in Hostettler et al. (2011) experienced partial remission of CNS sarcoidosis, 2 patients in Russell et al. (2013) had sustained clinical improvement in disease activity, and 9 patients with neurological complications in Van Rijswijk et al. (2013) showed improvement in fatigue severity and quality of life scores. In Panselinas et al. (2009), mental status and brain MRI improved and diabetes insipidus resolved with infliximab in 1 patient, tremors decreased in a second patient, and mental status and hydrocephalus improved in a third patient.

In Aguiar et al. (2011), 1 patient saw no improvement in neurological symptoms and discontinued infliximab. No response to treatment was seen in 1 patient in Chapelon-Abric et al. (2015), 1 patient in Hostettler et al. (2011) and 3 patients in Russell et al. (2013). In Panselinas et al. (2009), a patient with visual defects caused by CNS sarcoidosis also remained stable, although this patient only received 1 dose of infliximab.

Cutaneous sarcoidosis

Outcomes for 38 cases of refractory cutaneous sarcoidosis treated with infliximab, including 13 reported to be lupus pernio, were included in 9 of the studies (1 prospective study and 8 retrospective case reviews). Lesions resolved in 14 (37%), improved in 19 (50%), resolved or improved in 4 (with individual data for each outcome not reported, 11%) and remained stable in 1 (3%).

Lupus pernio resolved with infliximab in 1 patient in Doty et al. (2005) and 3 patients in Hostettler et al. (2011). Cutaneous sarcoidosis (non-lupus pernio or not reported as such) resolved in 1 patient in Chapelon-Abric et al. (2015), 2 patients in Ørum et al. (2012), 1 patient in Panselinas et al. (2009), 4 patients in Russell et al. (2013) and 2 patients in Sweiss et al. (2005).

All 4 patients with cutaneous sarcoidosis treated with infliximab in the prospective study by Vorselaars et al. (2015) had marked improvement or total resolution of skin lesions confirmed by photograph and clinical comparison.

In Aguiar et al. (2011), skin lesions improved significantly with infliximab in 1 patient with lupus pernio and disease became stable, without the need for further treatment. Lupus

pernio also improved with infliximab in 4 patients in [Doty et al. \(2005\)](#), 1 patient in [Hostettler et al. \(2011\)](#) and 2 patients in [Panselinas et al. \(2009\)](#).

In [Aguiar et al. \(2011\)](#), cutaneous plaques and 95% of cutaneous nodules disappeared in 1 person, and another had a 50% reduction in cutaneous nodules and experienced reduced pain from these. Improvement in cutaneous sarcoidosis was also seen in 1 patient in [Doty et al. \(2005\)](#), 7 patients in [Russell et al. \(2013\)](#) and 1 patient in [Sweiss et al. \(2005\)](#) treated with infliximab.

In [Panselinas et al. \(2009\)](#), lupus pernio remained unchanged following infliximab in 1 patient.

Ocular sarcoidosis

Thirteen patients with various manifestations of refractory ocular sarcoidosis were reported in 7 retrospective case reviews. Ocular sarcoidosis resolved with infliximab treatment in 3 patients (23%) and improved in 8 patients (62%); no change was seen in 2 patients (15%).

Symptoms resolved with infliximab in a person with chronic obstruction of both lachrymal glands in [Aguiar et al. \(2011\)](#). Remission was also seen in 1 patient in [Chapelon-Abric et al. \(2015\)](#) and 1 patient in [Russell et al. \(2013\)](#) with ocular sarcoidosis.

Eye pain improved in a patient with uveitis in [Doty et al. \(2005\)](#), and infliximab controlled ocular inflammation without the need for corticosteroids in 2 patients with uveitis and cystoid macular oedema in [Ørum et al. \(2012\)](#). Necrotising conjunctivitis and vision improved by 90% in a patient in [Sweiss et al. \(2005\)](#) and, in [Van Rijswijk et al. \(2013\)](#), vision improved in 4 patients with severe uveitis.

Two patients in [Russell et al. \(2013\)](#) experienced no change in ocular sarcoidosis with infliximab.

Lymph node sarcoidosis

Refractory lymph node sarcoidosis was reported for 14 patients who had infliximab in 4 retrospective case reviews. Of these, the disease resolved or improved in 6 (43%), was unchanged in 7 (50%) and deteriorated in 1 (7%).

Remission was seen with infliximab in 1 patient with sarcoidosis in the lymph nodes in [Chapelon-Abric et al. \(2015\)](#). In [Russell et al. \(2013\)](#), lymph node sarcoidosis resolved or improved in 3 patients. One patient with sarcoidosis in the lymph nodes in [Ørum et al. \(2012\)](#) reported subjective improvement in symptoms. In a patient with lymphadenopathy in [Sweiss et al. \(2005\)](#), lymph nodes in the neck resolved but those in the chest and abdomen only partially regressed.

In [Russell et al. \(2013\)](#) lymph node sarcoidosis was unchanged in 7 patients and worsened in 1 patient who received infliximab.

Bone, muscle and joint sarcoidosis

Across 5 retrospective case reviews of infliximab for refractory sarcoidosis, 4 patients had the disease in bones (1 in the bone marrow), 3 patients had it in muscles and 2 patients had it in joints. The sarcoidosis resolved with treatment in 3 patients (33%), improved in 5 patients (56%) and remained unchanged in 1 patient (11%). One patient who initially saw improvements subsequently worsened.

Single cases of bone and muscle sarcoidosis resolved with treatment in [Russell et al. \(2013\)](#) and remission was seen in 1 case with sarcoidosis in the joints in [Chapelon-Abric et al. \(2015\)](#).

In [Doty et al. \(2005\)](#), pain and swelling improved in a patient with myositis, although worsening was subsequently seen on MRI. In this study, a patient with sarcoidosis in the spine saw no improvement in symptoms with infliximab but the lesion became less conspicuous on MRI after treatment. Pain, oedema, induration and MRI findings improved in a patient with muscle sarcoidosis in [Panselinas et al. \(2009\)](#). Improvements on MRI were also seen in a patient with sarcoidosis in the spine. One patient with sarcoidosis in the bone marrow in [Ørum et al. \(2012\)](#) reported subjective improvement in symptoms.

Arthritis remained stable in a patient with sarcoidosis in the joints in [Panselinas et al. \(2009\)](#).

Cardiac sarcoidosis

Seven patients in 3 retrospective case series received infliximab for refractory cardiac sarcoidosis. Of these 4 (57%) experienced complete remission of the disease and 3 (43%) experienced partial remission.

In [Chapelon-Abric et al. \(2015\)](#), complete remission of cardiac sarcoidosis was seen with infliximab in 4 cases.

In the study by [Van Rijswijk et al. \(2013\)](#), after receiving infliximab, 2 patients with cardiac sarcoidosis experienced an improvement in left ventricular ejection fraction (from 37% to 60% and 35% to 45–50% respectively) and symptoms such as arrhythmias, palpitations, dizziness and/or dyspnoea on exertion. One patient in [Hostettler et al. \(2011\)](#) experienced partial remission.

Upper respiratory tract sarcoidosis

Refractory sarcoidosis in the upper respiratory tract was treated with infliximab in 6 patients reported in 4 retrospective case reviews. It resolved in 3 patients (50%), improved in 1 patient (17%) and remained unchanged in 2 patients (33%).

In [Sweiss et al. \(2005\)](#), signs and symptoms of nasal obstruction and sinusitis resolved completely in 3 patients with sarcoidosis in the upper respiratory tract who received infliximab.

Upper respiratory tract symptoms (particularly hoarseness) improved in 1 patient in [Doty et al. \(2005\)](#). One patient with sarcoidosis in the nose in [Ørum et al. \(2012\)](#) reported subjective improvement in symptoms.

Hoarseness, dysphagia and dyspnoea remained stable in a patient in [Panselinas et al. \(2009\)](#) and a case of sinus disease remained unchanged in [Russell et al. \(2013\)](#).

Hepatic and splenic sarcoidosis

Across 5 of the retrospective case reviews in the evidence summary, 2 patients had sarcoidosis in the spleen and 4 patients had sarcoidosis in the liver. The disease resolved with infliximab treatment in 2 patients (33%), improved in 2 patients (33%) and was unchanged in 2 patients (33%).

In [Aguilar et al. \(2011\)](#), 1 patient with splenomegaly had subjective improvement with infliximab but this could not be quantified and, in [Sweiss et al. \(2005\)](#), 1 patient experienced complete resolution of splenomegaly.

Remission was seen in 1 patient with liver sarcoidosis in the study by [Chapelon-Abric et al.](#)

(2015). Improved fatigue, pruritus and pain were experienced by a patient with liver sarcoidosis in [Doty et al. \(2005\)](#), and hepatomegaly and jaundice resolved. A patient with hepatic cirrhosis in [Aguiar et al. \(2011\)](#) continued to have abnormal laboratory test results and a patient in [Russell et al. \(2013\)](#) remained unchanged.

Other manifestations of sarcoidosis

A case of kidney sarcoidosis resolved with treatment in [Russell et al. \(2013\)](#). A further case with kidney sarcoidosis in [Ørum et al. \(2012\)](#) reported subjective improvement in symptoms.

One patient with sarcoidosis in the oesophagus in [Ørum et al. \(2012\)](#) reported subjective improvement in symptoms.

In [Van Rijswijk et al. \(2013\)](#), 7 patients with severe fatigue showed improvement in fatigue severity and quality of life scores.

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 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.

Observational studies

Adverse effects seen with infliximab in the observational studies included in this evidence summary were consistent with those listed in the [summary of product characteristics](#) (for example respiratory tract infections including pneumonia, headache, joint pain, oedema and rashes). Across the studies, about 15% of patients discontinued treatment due to adverse events.

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 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.

In the retrospective case series by [Aguilar et al. \(2011\)](#) (n=10), 2 patients did not complete a year of treatment, 1 due to lack of response, and the second due to non-infectious pneumonia. No other significant adverse effects were seen.

After a median of 6 infusions, 10/16 patients in [Chapelon-Abric et al. \(2015\)](#) discontinued infliximab: 7 due to infection, 1 due to paradoxical sarcoidosis, 1 due to leucoencephalopathy and 1 due to personal choice.

In [Doty et al. \(2005\)](#) (n=10), 1 patient experienced anaphylaxis with infliximab after taking it for over a year. Another developed angioimmunoblastic lymphoma, although a causal relationship with infliximab was not established. A patient who was also taking inhaled beclometasone developed oral candidiasis.

In [Hostettler et al. \(2011\)](#), 15/16 patients had no clinically relevant adverse effects with

infliximab over a mean of 29 months. After tolerating treatment for 4 years, 1 patient had bradycardia 6 hours after an infliximab infusion. The patient received a pacemaker and infliximab was restarted without recurrence of cardiac symptoms.

Two patients discontinued infliximab due to adverse effects in the study by [Ørum et al. \(2012\)](#) (n=12, mean duration 25 months).

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).

In [Sweiss et al. \(2005\)](#) (n=9), infliximab was discontinued in 1 patient due to drug-induced lupus, which resolved after treatment was stopped. The other 8 patients experienced no major adverse effects.

[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.

Adverse events were not reported in the study by [Panselinas et al. \(2009\)](#).

Evidence strengths and limitations

Observational studies are subject to bias and confounding and have many limitations affecting their application to clinical practice. The study by [Vorselaars et al. \(2015\)](#) was undertaken prospectively but was open-label. The other 9 studies were retrospective case series, which were generally undertaken in single centres. Other limitations of case series include differences in the management and follow-up of individual patients, inconsistent and incomplete recorded data, loss to follow-up and, potentially, missed patients.

All of the studies in the evidence summary were uncontrolled and, as is usual for rare diseases, had small sample sizes, particularly when considering the effects of infliximab on sarcoidosis in individual organs. The evidence summary included studies undertaken in people with extrapulmonary sarcoidosis in any organ, and excluded studies looking at sarcoidosis in a single organ. Therefore, it may not discuss the best available evidence for using infliximab in some individual manifestations of sarcoidosis. Nevertheless, the studies of individual organs identified in the searches for the evidence summary included few

patients and are unlikely to alter the findings substantially.

Neurological (n=52) and cutaneous (n=38) sarcoidosis were the most common manifestations of refractory extrapulmonary sarcoidosis treated with infliximab in the studies included in this evidence summary. These resolved or improved with treatment in the majority of patients. Specialists involved in the production of this evidence summary noted that, in people with severe and active refractory disease, even stabilisation of the sarcoidosis may be preferable to further deterioration. About 15% of patients in the studies discontinued infliximab because of adverse events.

The studies were undertaken in people with active, unstable sarcoidosis for whom corticosteroids and other treatments had proven ineffective, or who could not tolerate these treatments (refractory sarcoidosis). Therefore, the results cannot be generalised to people with stable disease or those who have not tried standard treatments. Although the studies are relevant to the overall UK population, some of them mainly included African-American people (for example, [Panselinas et al. 2009](#), [Russell et al. 2013](#) and [Sweiss et al. 2005](#)). Sarcoidosis has been shown to be more severe and difficult to treat in this population; nevertheless, many patients in these studies experienced what was considered to be a good response to infliximab.

The optimal dosage and treatment duration of infliximab for refractory extrapulmonary sarcoidosis is unclear because treatment regimens varied within and between the studies (typically infliximab 3 mg/kg or 5 mg/kg at weeks 0, 2 and 6, then at 4-, 6- or 8-weekly intervals for 6 to 46 months).

From the studies in the evidence summary it is unclear whether any benefits obtained with infliximab in the short-term will be maintained long-term. The study by [Panselinas et al. \(2009\)](#) followed patients who had discontinued infliximab for a mean of 12 months. At the end of the follow-up period, 12/14 patients deteriorated and 2/14 remained stable. [Chapelon-Abric et al. 2015](#) also reported that 3/11 patients deteriorated after stopping treatment. However, the searches undertaken for this evidence summary were not designed to identify studies of discontinuation of treatment and it is possible that other studies may be available.

Objective measures of treatment response were used where possible in most of the studies (for example, MRI for CNS sarcoidosis, photographs for cutaneous sarcoidosis, vision tests for ocular sarcoidosis and liver function tests for liver sarcoidosis). However, many of these are surrogate or disease-oriented outcomes, rather than patient-oriented

outcomes. Also, definitions of response to treatment were often not reported and may have varied across the studies, and the level of response was often determined by a single specialist clinician only. [Van Rijswijk et al. \(2013\)](#) and [Vorselaars et al. \(2015\)](#) found some statistically significant improvements in health-related quality of life but these are reported in the general study population, rather than in subgroups of people with individual manifestations of sarcoidosis.

According to specialists involved in this evidence summary, infliximab may be an option for some patients with severe, refractory extrapulmonary sarcoidosis (particularly cutaneous or neurological sarcoidosis); for example, those affected by disabling or disfiguring disease, or whose life expectancy is likely to be reduced.

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](#) (November 2016), a 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 3 mg/kg or 5 mg/kg at weeks 0, 2 and 6, then 6-weekly for 12 months. 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 12-month course of infliximab treatment

Infliximab dose ^a	Administration regimen	Cost of Flixabi ^b	Cost of Inflectra or Remsima ^b	Cost of Remicade
3 mg/kg, 240 mg	Weeks 0, 2 and 6, then 6-weekly for 12 months	£11,310.00	£11,329.80	£12,588.60

5 mg/kg, 400 mg		£15,080.00	£15,106.40	£16,784.80
<p>^a Based on treating an 80 kg person.</p> <p>^b 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.</p>				

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.

Expert advisers

Dr Michael Ardern-Jones, Associate Professor of Dermatology, University of Southampton

Dr Paul N Cooper, Consultant Neurologist, Greater Manchester Neuroscience Centre, Salford Royal Foundation Trust

Professor Nicholas Jones, Consultant Ophthalmologist and Director, Manchester Uveitis Clinic and Hon. Professor of Ophthalmology, University of Manchester, The Royal Eye Hospital

Dr Colm Leonard, Consultant Thoracic Physician and Honorary Senior Lecturer, University Hospital of South Manchester NHS Foundation Trust

Athol U Wells, Professor of Respiratory Medicine, Royal Brompton Hospital, London

Declarations of interest

Dr Paul N Cooper has modest holdings in pharmaceutical companies within funds that are managed on his behalf, without his involvement in decisions regarding transactions. Various pharmaceutical companies provide lunch to support his university department's weekly academic meeting. Bial Pharmaceuticals have offered to support Dr Cooper to attend a meeting in America.

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.

Dr Michael Ardern-Jones, Professor Nicholas Jones and 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.**

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