Clinical Commissioning Policy Proposition: Infliximab for Refractory or Progressive Neurosarcoidosis (Adults and post-pubescent children)

Reference: NHS England 1817

Prepared by NHS England Specialised Services Clinical Reference Group for Neurosciences

Published by NHS England, in electronic format only.

Contents

1 Executive Summary

Equality Statement

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

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About Neurosarcoidosis

Sarcoidosis can present in a variety of ways, ranging from a 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 lumps caused by clusters of inflammatory cells (non-caseating granulomas) in the organs. When the brain and central nervous system is affected, it is called neurosarcoidosis.

Neurosarcoidosis is an uncommon but potentially serious manifestation of the disease, which occurs in approximately 5% of people with sarcoidosis. Approximately 100 people are diagnosed with neurosarcoidosis in the UK each year (Sarcoidosis UK, 2018).

While the cranial nerves are most frequently affected, neurosarcoidosis can involve other nervous system tissues including the meninges (the membranes enclosing the brain and spinal cord); brain parenchyma (the functional brain tissue), especially the hypothalamic region; spinal cord; peripheral nerve and muscle. There is a specific subgroup of neurosarcoidosis involving the brain parenchyma which can cause

tissue destruction. This is the group of patients who are likely to benefit from infliximab, as it can prevent tissue destruction.

Neurosarcoidosis has no known cure. Spontaneous remission has been observed, but long-term therapy often is required. Treatment alleviates symptoms that are severe or progressive. Immunosuppression is the principal method of controlling the disease, and corticosteroids are the cornerstone of therapy.

About current treatments

Most patients with sarcoidosis do not require treatment and often make a full recovery. Around a third have more serious disease involving different organs and require therapies such as steroids and drugs that suppress the immune system. The majority of patients with neurosarcoidosis require treatment of some type, which may include steroids and oral immunosuppressants. In most cases this is all that is required to put patients into remission. However, in the invasive parenchymal form of neurosarcoidosis, these treatments have been shown to be ineffective.

About the new treatment

Infliximab belongs to a group of medicines called ‘biological drugs.’ It is a type of drug which works by reducing the effect of a chemical called tumour necrosis factor-alpha (TNF- α). TNF- α is released in response to a disease or infection as part of the body’s immune response. Infliximab is used to treat a number of medical conditions including Crohn’s disease, ulcerative colitis and certain types of arthritis such as rheumatoid arthritis and ankylosis spondylitis.

What we have decided

NHS England has carefully reviewed the evidence to treat refractory or progressive neurosarcoidosis with infliximab. We have concluded that there is enough evidence to consider making the treatment available.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission infliximab for refractory or progressive neurosarcoidosis.

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

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether infliximab for refractory or progressive neurosarcoidosis will be routinely commissioned will made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

Sarcoidosis is a systemic granulomatous disease of unknown cause characterised by multi-organ involvement. Almost 90% of patients have lung involvement but many of these will also show involvement of other organs, typically the skin and eyes (uveitis). Around 1 in every 10,000 people have sarcoidosis in the UK. Incidence is highest in people aged 30 to 50 years and appears to be higher in Afro-Caribbean people and marginally higher in women (Sarcoidosis UK, 2018). Overall mortality in sarcoidosis is 1%-5%, usually due to pulmonary, cardiac or neurological involvement or their complications (Sarcoidosis UK, 2018).

Neurological sarcoidosis is uncommon and occurs in approximately 5% of people with sarcoidosis. About 100 people are diagnosed with neurosarcoidosis affecting the brain and spinal cord in the UK each year (NICE Evidence Review, 2018). It can affect the central nervous system (CNS, the brain and spinal cord) and peripheral nervous system (including the 12 cranial nerves supplying the head and neck). When the nerves are affected there may be weakness, numbness of the face, problems with hearing, weakness of the tongue, difficulty swallowing, or double vision. Other patients have more serious disease affecting the CNS such

as meningoencephalitis (inflammation of the lining of the brain and spinal cord) or vasculitis (inflammation of the blood vessels in the brain).

Usually, oral corticosteroids are the first line therapy for patients with progressive disease or significant symptoms, with a maintenance dose given for 6-24 months. Other immunosuppressive or anti-inflammatory treatments are considered when corticosteroids are failing to control disease, the side effects are intolerable, or corticosteroids are contraindicated (typically when patients also have diabetes mellitus and osteoporosis). Methotrexate or azathioprine are the most common second line treatments (Warrell et al, 2014).

In neurosarcoidosis, around 80% (80 people) respond to 1st line and 2nd line oral treatment but around 20% (20 people) need further treatment (NICE Evidence Review, 2018).

Infliximab has been used in the treatment of neurosarcoidosis that does not respond to first, or second line treatments. Infliximab works by reducing the effect of a chemical called tumour necrosis factor- alpha (TNF- α), which is released in response to disease or infection as part of the body's immune response. It is currently licensed as a treatment for other immune mediated diseases such as rheumatoid arthritis and Crohn's disease (Sarcoidosis UK, 2018). However, Infliximab does not have a license or marketing authorisation for sarcoidosis.

A review of the current literature of infliximab in the treatment of neurosarcoidosis has been carried out and informs the development of this clinical commissioning policy.

4 Definitions

Sarcoidosis – a systemic granulomatous disease of unknown cause characterised by multi-organ involvement.

Neurosarcoidosis - sarcoidosis affecting the central nervous system including the brain and spinal cord.

Leptomeningitis - inflammation of the tissues surrounding the brain or spinal cord.

Pachymeningitis - a rare illness which can be shown by MRI imaging to be a thickening of the tissue surrounding the brain and spinal cord when associated with an infectious, malignant or rheumatic systemic disease.

Refractory neurosarcoidosis - neurosarcoidosis that has failed to respond to standard treatments (for example, corticosteroids and immunosuppressants).

Progressive neurosarcoidosis - sarcoidosis affecting the brain and spinal cord which is progressively worsening, despite first and second line treatments.

Infliximab - a drug which works by reducing the effect of a chemical called tumour necrosis factor- alpha (TNF- α). TNF- α is released in response to a disease or infection as part of the body's immune response.

5 Aims and Objectives

This policy proposition considered: the clinical circumstances in which NHS England might commission and fund the use of infliximab in the treatment of refractory or progressive neurosarcoidosis.

The objectives were to:

- assess the evidence for the clinical effectiveness, safety and cost effectiveness of infliximab in the treatment of refractory and/or progressive neuro sarcoidosis; and
- clarify the commissioning position of NHS England and ensure equitable use of infliximab as a treatment for patients with refractory and/or progressive neurosarcoidosis.

6 Epidemiology and Needs Assessment

The cause of sarcoidosis is unknown. It is characterised by nodules of inflammation (non-caseating granulomas) and scarring in affected organs.

Around 1 in every 10,000 people in the UK has sarcoidosis. The incidence is highest in people aged 30 to 50 years and appears to be higher in Afro-Caribbean people and marginally higher in women (Sarcoidosis UK). Sarcoidosis in children is extremely rare. Many infectious and neoplastic diseases can simulate sarcoidosis.

The presentation of sarcoidosis varies considerably from mild, acute self-limiting disease to chronic disease involving several organs and causing severe symptoms and functional impairment. The most commonly affected organ is the lung, which is affected in more than 90% of people with sarcoidosis.

The natural course of sarcoidosis is difficult to predict and there are significant differences in the severity of disease and the organs involved. The prognosis is generally good and sarcoidosis resolves in most people within two to five years.

It is estimated that 5-10% of cases have neurological involvement (Sarcoidosis UK). The NICE Evidence Review (2018) suggests about 100 people are diagnosed with neurosarcoidosis affecting the brain and spinal cord in the UK each year. Patients with neurosarcoidosis have a particularly poor prognosis and present with severe acute events, e.g. optic neuritis and blindness, acute hydrocephalus and coma or progressive lower limb weakness (Sarcoidosis UK). Around 80% respond to 1st and 2nd line oral treatment, but around 20% need further treatment.

Disease related mortality in sarcoidosis is reported to be about 5%, with the most common cause of death being from lung, cardiac and neurological disease that is refractory to therapy (Warrell et al, 2014).

7 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

This evidence summary considers the best available evidence for infliximab (alone or in combination with other medicines) for treating neurosarcoidosis that is refractory to standard treatments (for example, corticosteroids and immunosuppressants) or is progressive despite current treatments.

Sarcoidosis is characterised by the presence of clusters of inflammatory cells in affected organs (non-caseating granulomas). Neurosarcoidosis is a rare type of sarcoidosis that affects the central nervous system (CNS, brain and spinal cord) causing meningoencephalitis and vasculitis.

The evidence review focused on 2 multicentre retrospective case reviews undertaken in the USA (Gelfand et al. 2017, n=66) and France (Jamilloux et al. 2017, n=132, 63 with neurosarcoidosis). In summary, the results of the studies suggest that infliximab can improve outcomes for some people with refractory or progressive neurosarcoidosis, with many people reported as experiencing a complete or partial response. However, some people had residual symptoms and functional impairment after treatment, or experienced no response to treatment. Also, adverse effects of infliximab were sometimes serious and led to hospitalisation or discontinuation of treatment. Relapse of neurosarcoidosis appears to be common on stopping infliximab. See below for more details.

When assessing images obtained using magnetic resonance imaging (MRI), Gelfand et al. found that, in people using infliximab for 1.5 years on average, neurosarcoidosis resolved completely in 52% (29/56), partially improved in 30% (17/56), stayed the same in 14% (8/56) and got worse in 4% (2/56). When people were assessed by their specialist after using infliximab, Gelfand et al. found that clinical signs and symptoms of neurosarcoidosis resolved completely in 29% (19/66), partially improved in 48% (32/66), stayed the same in 18% (12/66) and got worse in 3% (2/66). A favourable response with complete or partial recovery was seen in 80% of people (45/56) who had evaluations for both clinical response and MRI findings. This suggests that 8 out of 10 people experienced some improvement in both findings on MRI and clinical signs and symptoms.

In the study by Gelfand et al., neurosarcoidosis recurred in 56% of people (9/16) who had experienced remission after using infliximab for, on average, 1.5 years. Relapse occurred, on average, about 6 months after treatment was stopped. These results suggest that around half of people with neurosarcoidosis experience relapse when they have been treated with infliximab for about 1.5 years.

Gelfand et al. found that combination therapy of infliximab with another immunosuppressant was associated with higher odds of a favourable treatment response (adjusted OR 6.9, 95% CI 1.2 to 41.3, p=0.03)

In the study by Jamilloux et al., a tool was used to assess the severity of sarcoidosis in various organs in the body. The average severity score for the CNS changed from 3.78 to 2.62 after treatment with an anti-TNF (usually infliximab) in 63 people with neurosarcoidosis (p=0.001). This shows that people's score improved by 1.16 on a 6-point scale, which suggests that, on average, their neurosarcoidosis improved. However, although individual people may feel quite a large benefit, others may experience no benefit, and it is unclear if a 1 point improvement is large enough to be important to the overall population with neurosarcoidosis.

Overall, the studies suggest that, when infliximab is used for neurosarcoidosis, its adverse effects are similar to those that are seen when it is used for the licensed indications, as listed in the summary of product characteristics; for example, infections are common and may lead to hospitalisation or discontinuation of treatment.

The results of the studies should be interpreted with caution because the studies are small, uncontrolled, and did not use standardised treatment and monitoring protocols. Weaknesses in the studies' design and conduct mean they are subject to bias and confounding, are difficult to interpret and cannot support firm conclusions.

The optimal treatment regimen for infliximab for treating neurosarcoidosis is unclear because treatment regimens varied within and between the studies. The dosage of infliximab typically used was 3 to 7 mg/kg at weeks 0, 2, and 6, then every 6 to 8 weeks. The median duration of treatment in the key studies was between about 1.5 years and 1.7 years. Most people in the studies took corticosteroids and/or immunosuppressants in combination with infliximab, and it is unclear how this affects outcomes. It is also unclear what potential factors predict a good response to Infliximab treatment.

8 Proposed Criteria for Commissioning

Eligibility Criteria

Patients must have a confirmed diagnosis of neurosarcoidosis:

- Histological proof of systemic sarcoidosis in patients who present with neurological impairment compatible with a diagnosis of neurosarcoidosis, confirmed via MRI.

  OR
- Patients presenting with isolated neurosarcoidosis, where there is no evidence for sarcoidosis in the systemic organs and a biopsy of neurological tissue yields evidence of granulomatous inflammation and no evidence of any alternative diagnosis (such as infection, tumour or other inflammatory disease)

  OR
- The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations of MRI/Cerebrospinal Fluid (CSF) and/or Electromyography (EMG)/ Nerve Conduction Studies (NCS) findings typical of granulomatous inflammation of the nervous system after rigorous exclusion of other causes

  ALL patients must have had an infectious or neoplastic disease cause excluded.

Treatment starting criteria

Infliximab will be added to a neurosarcoidosis treatment regimen including high dose steroids and oral immunosuppressants in adult and post-pubescent patients with progressive and refractory disease who fulfil the following criteria:

- Patients with an abnormal MRI compatible with pachymeningitis or leptomeningitis (i.e. imaging evidence of enhancement and inflammation of the meninges and adjacent brain and/or spinal cord, cranial nerves and nerve roots within the spinal canal) with an examination of the cerebrospinal

fluid which has ruled out a superimposed infection or neoplastic disease who:

- have severe, aggressive disease with risk of rapid, permanent and profound neurological impairment early in their disease;
  AND
- have failed to respond to high dose steroids and other oral immunosuppressants;
  OR
- are unable to be treated with high dose steroids and oral immunosuppressant agents due to severe intolerance or toxicity.

Patients must be managed at, or in collaboration with, a centre commissioned to provide specialised services that has expertise in the assessment and management of neurosarcoidosis. Patients who satisfy the eligibility criteria will be eligible for treatment with Infliximab.

Exclusion Criteria

- History of Tuberculosis (TB)
- Any evidence of concurrent TB, fungal, viral or parasitic infection; HIV, hepatitis, active herpes simplex virus (HSV), vesicular stomatitis virus (VZV), cytomegalovirus (CMV) or Epstein-Barr virus (EBV)
- Any evidence of current infection that may deteriorate with treatment
- History of demyelinating disease
- History of malignancy including malignant myeloma
- History of moderate or severe heart failure (this is NYHA class III/IV)

Dosing

The infliximab biologic with the lowest acquisition costs should be used. This is likely to be an infliximab biosimilar.

The recommended infliximab treatment dose regimen for adults and post-pubescent children with neurosarcoidosis is induction at 0, 2 and 6 weeks at a

dose of 5mg/kg. Thereafter, it is given every 4-8 weeks at a dose of 5mg/kg. It is given in hospital by intravenous infusion and can be given as a day case.

All patients will undergo an MRI every three months or earlier if required. All patients will have monitoring of serum infliximab levels and antibody formation prior to every infusion and will undergo regular monitoring for any adverse events at each appointment.

Stopping Criteria

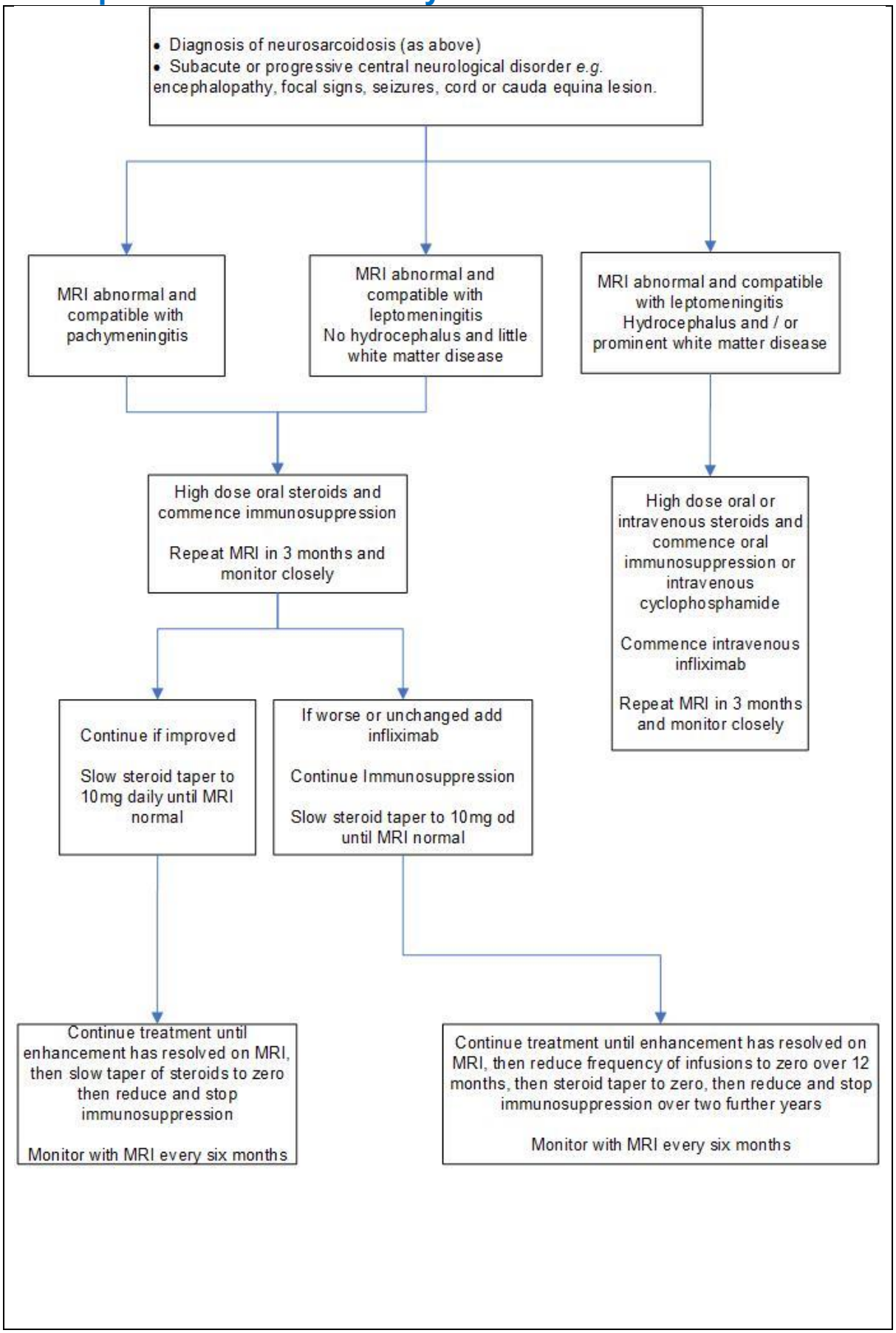
A decision to stop using Infliximab for neurosarcoidosis should be made by a multidisciplinary team (MDT) at a UK specialist centre, using the following criteria:

- For patients who respond and achieve drug-induced disease remission achieving full resolution of enhancement on MRI, infusions of infliximab should then be reduced in frequency to zero over a period of 12-18 months.
- If there is no improvement seen on MRI within six months.
- If there are any adverse events where harm exceeds the benefit.

Criteria for repeat treatments

Re-treatment of such patients is permitted if the clinical assessment confirms that there is clinical evidence of a flare, in addition to evidence of enhancement on an MRI.

9 Proposed Patient Pathway



10 Proposed Governance Arrangements

Any provider organisation treating patients with this intervention will be required to provide assurance that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics Committee (or similar) and NHS England may ask for assurance of this process. Each provider organisation treating children with a medicine approved under the policy 'Commissioning Medicines for Children in Specialised Services' (https://www.england.nhs.uk/wp-content/uploads/2017/03/commissioning-medicines-children-specialised-services.pdf) will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics Committee (or similar) and NHS England can ask for documented evidence that these processes are in place.

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

11 Proposed Mechanism for Funding

Reimbursement for use of infliximab for patients with refractory or progressive neurosarcoidosis meeting the criteria in this policy is provided via specialised commissioning teams.

The cost will depend on the infliximab product used, the price of which is commercial in confidence. Only the infliximab product with the lowest acquisition cost will be reimbursed under this policy (likely to be a biosimilar).

12 Proposed Audit Requirements

Access to infliximab would be provided through specialised neuroscience centres with access to specialists in this field.

Software systems will be used to track and audit use of infliximab by clinicians, in order to ensure it is administered according to the Criteria for Commissioning.

Patients will be registered under a national database that will be created in order to monitor the number of patients accessing treatment and the relevant outcomes. There will be strict monitoring of data collection in each of these centres.

13 Documents That Have Informed This Policy Proposition

Gelfand JM, Bradshaw MJ, Stern BJ, et al. (2017) Infliximab for the treatment of CNS sarcoidosis: a multi-institutional series. Neurology 89(20), 2092–100

Jamilloux Y, Cohen-Aubart F, Chapelon-Abric C, et al. (2017) Efficacy and safety of tumor necrosis factor antagonists in refractory sarcoidosis: A multicenter study of 132 patients. Seminars in Arthritis and Rheumatism 47(2), 288–94

14 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or not for routine commissioning.

15 References

Sarcoidosis UK. (2018). Sarcoidosis UK Homepage - Information, Support, Awareness and Research into Sarcoidosis. [online] Available at: https://www.sarcoidosisuk.org [Accessed 29 Nov. 2018].

Warrell, D. Cox, T. Firth, J. and Török, E. (2014). Oxford Textbook of Medicine. Oxford: OUP Oxford.

National Institute for Health and Care Excellence. 2017. Refractory extrapulmonary sarcoidosis: infliximab. January 2017.

END