AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence Status Report: mepolizumab (Nucala®▼) for the treatment of chronic eosinophilic pneumonia.
November 2019

KEY FINDINGS

Report background
Chronic eosinophilic pneumonia (CEP) is a rare disease that is part of a larger group of lung diseases characterised by abnormal infiltrations of eosinophils in the lungs. It is characterised by the progressive onset of symptoms including cough, dyspnoea, malaise, chest pain, fever and weight loss, over a few weeks. It is usually successfully treated with corticosteroids but the disease can relapse on tapering or discontinuation of corticosteroids. There are no published guidelines for mepolizumab's use as a treatment for chronic eosinophilic pneumonia and its use for this indication is off-label. Clinicians in Wales consider there is an unmet need and have identified a cohort of patients who could benefit from this treatment. This medicine was therefore considered suitable for assessment via the One Wales process.

Efficacy/Effectiveness
The evidence of clinical effectiveness of mepolizumab to treat CEP comes from individual case studies and anecdotal evidence from the submitting clinician. Most of the case studies showed improvements in symptoms and allowed patients to taper or completely stop corticosteroid treatment.

Safety
There were no serious safety concerns reported in the included case studies however there had been one injection site reaction followed by a mild anaphylactic reaction after which the patient was switched to an alternative IL-5 antibody.

Patient factors
Mepolizumab is administered every four weeks by subcutaneous injection by a healthcare professional.

Cost effectiveness
There are no studies on the cost effectiveness of mepolizumab as second-line treatment of CEP. Cost effectiveness analyses from the NICE technology appraisal of mepolizumab for the treatment of eosinophilic asthma are provided as a proxy. The base case incremental cost effectiveness ratio (ICER) was based on exacerbation rates which is not directly transferable to CEP but other factors of both conditions may be suitably comparable. The most plausible ICER for this indication was £29,163 based on a simple patient access scheme (PAS) price.

Budget impact
Specialist clinicians consulted by AWTTC estimate that there are currently 35 people eligible to receive mepolizumab in this setting with an additional seven becoming eligible per year . Of the proportion of people who would respond to treatment it is assumed that they would remain on treatment for at least three years. This is associated with an annual cost of £236,303-236,450 in Year 1 and of £258,096-259,858 in Year 3, depending on treatment response rates. [Confidential information removed]. The budget impact is subject to significant uncertainty.

Welsh commercial access agreements
This medicine is currently not licensed for the indication under consideration (i.e. off-label) and therefore as the Pharmaceutical Industry's code of practice prevents a company from promoting an off-label use of a medicine, a commercial agreement cannot be offered by the company.

Impact on health and social care services
The impact on services is considered to be minimal.

Innovation and/or advantages
Mepolizumab represents an option for when chronic eosinophilic pneumonia cannot be effectively treated by corticosteroids or for people who cannot tolerate high dose/chronic corticosteroid treatment and require a steroid-sparing treatment option.

BACKGROUND

Target group

The indication being considered is the treatment of chronic eosinophilic pneumonia (CEP), as an alternative to off-label azathioprine or mycophenolate in patients who require chronic or repeated corticosteroid courses. There are no medicines currently licensed for the second line treatment of CEP.

Technology

Mepolizumab is a humanised monoclonal antibody which targets interleukin-5 (IL-5)[1]. IL-5 is the major cytokine responsible for the growth, differentiation, recruitment, activation and survival of eosinophils. Mepolizumab inhibits the bioactivity of IL-5, inhibiting IL-5 signalling and reducing the production and survival of eosinophils[1].

Marketing authorisation date

Mepolizumab is not licensed to treat CEP; its use in this indication is off-label. Mepolizumab (Nucala®▼) is licensed as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged six years and older[1].

Dosing

There is no agreed dosing regimen for mepolizumab to treat CEP. The recommended dose for eosinophilic asthma is 100 mg administered subcutaneously every 4 weeks[1]. Although limited to individual case studies, the dosing regimens used in the literature for CEP align with that outlined in the summary of product characteristics [1-4]. The duration of treatment has not been defined.

Clinical background

CEP is a rare disorder among the diffuse parenchymal lung diseases[5]. These diseases are characterised by abnormal infiltrations of eosinophils in the lungs. There are no symptoms specific to CEP. Prolonged (several months) respiratory symptoms such as cough (60-90%) and shortness of breath/dyspnoea (20-50%) are the most common manifestations but patients rarely develop respiratory failure and usually show normal or mild hypoxemia. Patients may also exhibit appetite/weight loss and chest pain[5].

Diagnostic criteria include: alveolar eosinophilia ≥ 40% of the total cell count at bronchoalveolar lavage (BAL) or peripheral blood eosinophilia ≥ 1000/mm^3; peripheral alveolar opacities at chest imaging; respiratory symptoms present ≥ 2- 4 weeks; absence of other eosinophilic lung disease causes[6-9].

CEP can develop at any age but most patients with CEP are 30–50 years old; women are twice as likely to develop it[5,8]. More than half of those with CEP have an allergic disease such as asthma, allergic rhinitis or atopic dermatitis[8]. Approximately 75% of patients

experience asthma at some time throughout the course of the disease[7]. Most patients are non-smokers (> 60%)[5].

Prognosis is excellent for most patients with CEP[10]. This is despite the risk of relapse and the occasional need for long-term treatment. Relapse does not appear to indicate treatment failure or a worse prognosis as CEP generally continues to respond to corticosteroids at levels similar to those prior to relapse. Some patients have demonstrated more accelerated respiratory failure when diagnosis has been delayed or missed and CEP has occasionally led to irreversible fibrosis[10,11].

Incidence/prevalence

The precise number of people with CEP is not well defined. A small retrospective study (n = 10) estimated the annual incidence of CEP at 0.23 cases per 100,000 people per year in a European population[12]. Towards the end of the 14 year study period the incidence increased to 0.54 cases per 100,000 people per year[12]. This would equate to 8–17 patients in Wales.

A specialist clinician consulted by AWTTC estimates that there are five patients with CEP per health board who may currently be suitable for treatment with mepolizumab, equating to 35 patients in Wales. They estimate that one or fewer new patients per year per health board may subsequently be suitable for treatment, equating to up to seven new patients per year across Wales.

Current treatment options

The management goal of CEP is to control the disease with the smallest dose of corticosteroids to minimise the likelihood of relapse and corticosteroid-related adverse effects (AE)[13]. There is no consensus on the doses or duration of corticosteroid treatment, initial doses of prednisone start between 0.5 and 1 mg/kg per day followed by a gradual tapering of the dose for a total treatment duration of 6–12 months[8]. CEP is also characterised by its dramatic and prompt resolution with corticosteroid treatment; if a patient does not respond well to corticosteroid treatment, an alternative diagnosis should be considered[5,8,11,13].

Markers of disease improvement in CEP include the resolution of presenting symptoms (dyspnoea, cough, etc.), a decline in peripheral blood eosinophilia, a marked reduction or clearing of chest imaging abnormalities (although these may persist for longer on computed tomography (CT) scans) and physiologic improvement in pulmonary function testing parameters[10].

Approximately 50% of patients relapse, often while tapering corticosteroid dose or after weaning[8]. More than half of patients may require long-term, even lifelong, corticosteroids due to multiple relapses or severe asthma[8]. Inhaled corticosteroids are often used, particularly as patients also have asthma, and may reduce the need for long-term oral corticosteroids[6]. Reliance on corticosteroids has led to efforts toward finding alternative corticosteroid reducing therapies for patients requiring long-term treatment[14].

A specialist clinician consulted by AWTTC indicated that, to reduce corticosteroid burden, adding an alternative immunosuppressive drug to corticosteroid treatment, usually azathioprine or mycophenolate, was another management option. They noted that this can expose a patient to the risks of immunosuppression, myelosuppression and liver failure.

There are no licensed treatments for CEP. Biologic medicines other than mepolizumab are also licensed for the treatment of severe eosinophilic asthma and may be of therapeutic benefit in CEP but evidence is limited. These include the IL-5 antibodies, reslizumab and

benralizumab[5,14]. The anti-IgE antibody, omalizumab, is licensed for the treatment of IgE mediated asthma (IgE is sometimes raised in CEP) and has also been used for the treatment of CEP[5,14].

Guidance and related advice

There is currently no published guidance relating to the treatment of CEP.

SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

A comprehensive literature search conducted by AWTTC, together with conference abstracts identified by the submitting clinician, identified three case studies of individual patients and four conference abstracts of mepolizumab to treat CEP. These studies are briefly described below.

Efficacy

Individual case studies:
To et al. (2018) reported a case of a 65-year-old man who presented with a chronic cough and abnormal chest X-rays[4]. He had a 20-year history of bronchial asthma and had never smoked. He had elevated eosinophilia at BAL (72%), elevated peripheral eosinophilia, abnormalities on chest CT and other eosinophilic lung diseases were excluded. He was diagnosed with CEP and started on prednisolone 30 mg daily (0.5 mg/kg/day) with biweekly tapering. He responded well and symptoms disappeared with decreasing peripheral eosinophil counts. After corticosteroids were terminated, his symptoms worsened and peripheral eosinophilia returned; the CEP had relapsed. Due to the adverse events associated with long-term corticosteroid treatment, the patient was started on mepolizumab 100 mg every month. After one month, peripheral eosinophil counts had decreased to the normal range and his symptoms had disappeared. At 13 months the patient had no relapse of CEP, the treating physicians planned to continue mepolizumab with careful observation[4].

Sarkis et al. (2018) reported a case of a 42-year-old woman with type II diabetes and a history of smoking who had a chronic cough, a low grade intermittent fever, dyspnoea, right-sided pleuritic chest pain and poorly responsive to multiple courses of antibiotics[2]. She required mechanical ventilation on arrival at the hospital. She had elevated eosinophilia at BAL (48%), abnormalities on chest CT and other lung diseases were excluded. She was diagnosed with CEP and started on corticosteroids 0.5 mg/kg. She responded well; mechanical ventilation was no longer required after 48 hours and chest CT abnormalities were resolved after one month of treatment. Tapering was attempted but resulted in four relapses of CEP over 18 months. She experienced a number of corticosteroid adverse effects. The patient was started on mepolizumab 100 mg every four weeks. Symptoms disappeared after two weeks of treatment alongside corticosteroid tapering and her peripheral eosinophil count returned to the normal range. Six months after initiating mepolizumab the patient experienced an injection site reaction followed by a mild anaphylactic reaction consisting of a feeling of glottis closure. She was switched to a different IL-5 antibody, reslizumab 3 mg/kg infusion every four weeks. After two months of this treatment she was able to cease corticosteroid treatment. Seven months after initiating reslizumab the patient experienced a relapse and corticosteroid treatment was restarted. At time of publication the corticosteroids were being tapered again[2].

Lin et al. (2019) reported a case of a 48-year-old woman, presenting in June 2010 with a three-year history of respiratory symptoms including pneumonia and a history of prior smoking[3]. On examination wheezing was heard in both lungs, she was found to have poor pulmonary function and was started on an inhaled corticosteroid, montelukast and bronchodilators. In October 2010 abnormalities were present on chest CT and lung biopsy,

she was diagnosed with CEP and commenced on prednisolone (5–30 mg/day). When measured in December 2010, peripheral blood eosinophilia was low. Due to corticosteroid adverse events, methotrexate 5 mg/week was started as a steroid sparing strategy in early 2013, but this treatment was discontinued due to lack of efficacy (hypoxemia for which she had started home oxygen therapy) the following year. The patient was started on omalizumab 150 mg subcutaneously every four weeks in September 2015. The following June, abnormalities on chest CT had increased as well as peripheral eosinophilia. In September, omalizumab was discontinued and mepolizumab 100 mg subcutaneously every four weeks was started. Symptoms and pulmonary function started to improve and the following year the patient no longer required oxygen supplementation. In February 2018, the abnormalities on chest CT had nearly fully resolved and peripheral eosinophilia was low. By July of that year the patient had not been using oral corticosteroids for two months and had received treatment with mepolizumab for 22 months[3].

Individual conference abstracts:
Taylor et al. (2016) reported a case of a 27-year-old woman who had a several year history of recurrent CEP with declining lung function, was steroid dependent and was refractory to azathioprine and mycophenolate mofetil[15]. Regular mepolizumab (dose not reported) infusions enabled a complete remission from CEP without the use of corticosteroids[15].

Lam et al. (2016) reported a case of a 49-year-old woman who had a year-long history of dry cough which was responsive to intermittent corticosteroid treatment[16]. She was a non-smoker. She had elevated eosinophilia at BAL (92%), elevated peripheral eosinophilia and abnormalities on chest CT. She was diagnosed with CEP and started on corticosteroids 60 mg/day but was unable to taper below 20 mg. The patient was started on mepolizumab (dose not reported) and this allowed successfully tapering of corticosteroids to 10–20 mg/day[16].

Lawrence et al. (2019) reported a case of a 49-year-old man who had a year-long history of worsening dyspnoea and productive cough[17]. He had previously used tobacco. He had abnormalities on chest CT but no peripheral or BAL eosinophilia. A lung biopsy demonstrated CEP and he was diagnosed with CEP. He was started on corticosteroids 40 mg/day and this significantly reduced symptoms but tapering below 20 mg/day was unsuccessful. Mepolizumab (dose not reported) in addition to vedolizumab (a gut-selective immunosuppressant for his ulcerative colitis) was started. Improvement in symptoms occurred within seven days of initiating treatment. Six months later, chest abnormalities had improved and the patient no longer used corticosteroids[17].

Jones et al. (2019) reported a case of a 55-year-old woman who had a history of asthma and presented with worsening cardiopulmonary complaints[18]. She had peripheral eosinophilia (31.2%), the presence of alveolar infiltrates and BAL eosinophilia (86%) and was diagnosed with CEP. Whilst on treatment she developed psychiatric symptoms related to high dose corticosteroid use which prompted their rapid tapering for mepolizumab (300 mg every four weeks). Mepolizumab alongside low dose corticosteroids enabled adequate symptom control[18].

Safety

In the clinical trials for the treatment of eosinophilic asthma, the most common adverse event associated with mepolizumab treatment reported in ≥ 1 in 10 people, was headache[1]. The next most commonly reported adverse events, reported in ≥ 1 in 100 people to < 1 in 10 people, included injection site reactions, back pain, infection, eczema, upper abdominal pain, nasal congestion and hypersensitivity reactions[1].

In the studies evaluated for this report, and for which information was provided and attributed to mepolizumab, there were no adverse events reported except for one patient. Sarkis et al.

(2018) reported an injection site reaction followed by a mild anaphylactic reaction consisting of a subjective feeling of glottis closure after which the patient was switched to a different IL-5 antibody[2].

Clinical effectiveness issues

- Mepolizumab is being considered for this patient group because of the potential yet unconfirmed role played by IL-5 in the development of CEP. IL-5 release from Th2 cells that had migrated to the lungs triggers the influx and accumulation of eosinophils to the lungs. As an antibody that binds IL-5, mepolizumab is a treatment that targets this aspect of CEP pathogenesis, diminishing lung eosinophilia.
- There are no randomised control studies or systematic reviews investigating the use of mepolizumab to treat CEP. The evidence is pulled from individual case studies and anecdotal evidence from the submitting clinician.
- There is no published treatment protocol or recommended dose of mepolizumab to treat CEP. The evidence from case studies indicates that the licensed dose for mepolizumab for treating severe refractory eosinophilic asthma, 100 mg subcutaneously every four weeks, is most widely used by clinicians. When reported, treatment duration varied widely in the studies, ranging from 1–22 months (both at time of publication). It is difficult to get a consensus timeframe for treatment other than to continue mepolizumab use under careful observation.
- The case studies were varied in terms of criteria used for CEP diagnosis, the treatment pathways taken and the markers of disease improvement used.
- Patients with CEP presented in the case studies often had co-morbidities such as asthma.
- Most often, mepolizumab alleviated the symptoms of CEP within the included case studies and enabled patients to taper or completely stop corticosteroid treatment. However, there was a case where a patient receiving mepolizumab experienced an injection site reaction followed by a mild anaphylactic reaction and the patient was switched to a different IL-5 antibody.
- There are significant risks associated with long-term corticosteroid treatment including serious infections, the development of Cushingoid features, reduction in bone mineral density and early cataracts. Corticosteroid adverse events were reported in some of the case studies here and were an influential factor in patients being offered a treatment alternative.

SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

There are no studies on the cost-effectiveness of mepolizumab for the treatment of CEP. In the absence of information a brief description of the cost effectiveness analyses from the NICE technology appraisal for the treatment of eosinophilic asthma are provided as a proxy[19]. A simple patient access scheme (PAS) was included providing the medicine at a discount to the list price. The cost effectiveness of mepolizumab was compared to standard of care for asthma patients. A Markov model was provided by the company with base case and scenario analyses, the NICE evidence review group (ERG) also conducted a base case analyses using the Appraisal Committee's preferred assumptions[20]. The NICE ERG analyses will be provided in this section along with the associated limitations. On consultation with clinical experts the rationales for this approach are as follows:

- The dose of mepolizumab used for treatment of CEP would be the same as the recommended dose for eosinophilic asthma.
- The mean age used in the model for commencing treatment in the eosinophilic asthma patients is considered comparable to the expected age for CEP patients.
- The treatment duration is considered comparable between the two diseases with the attrition (burn out) rate and proportion of patients remaining on lifelong treatment similar.
- Hospital or emergency room admission rates are considered comparable.
- The quality of life for patients with these conditions would be considered similar with comparable benefits on treatment and decrements in terms of treatment side effects and exacerbations or relapse in their conditions.
- Re-instatement or an increase in oral corticosteroids would be the treatment option for both eosinophilic asthma exacerbations and relapse of CEP.

Data from two placebo-controlled clinical trials, DREAM and MENSA and a prospective study by Lloyd et al on the impact of asthma exacerbations on quality of life were used to derive utility values[21-23]. An open-label extension study, COSMOS, was used to provide rates for continuation of treatment[24]. The model used a lifetime treatment duration and the ERG calculated base cases for three scenarios using different criteria for continuation of treatment: no worsening of asthma exacerbations; 30% exacerbation reduction; 50% exacerbation reduction[20]. The most plausible base case for each scenario is shown in Table 1. Sensitivity analyses on age at start of treatment and treatment effect duration were also provided, the results are shown in Table 2.

Table 1. Results of the NICE evidence review group's most plausible base case for mepolizumab versus standard of care[20]

	Most plausible base case
No worsening of exacerbation	£31,895
30% exacerbation reduction	£31,378
50% exacerbation reduction	£29,163

Table 2. Most plausible base cases from the NICE evidence review group's sensitivity analyses for mepolizumab versus standard of care[20]

	Age (years) at treatment start			Treatment effect duration (years)			
	40	45	51.5*	10	20	30	Lifetime*
No worsening	£44,298	£35,988	£31,895	£44,582	£39,995	£37,419	£31,895
30% reduction	£42,750	£34,927	£31,378	£46,784	£39,817	£37,081	£31,378
50% reduction	£39,761	£32,557	£29,163	£43,429	£37,392	£34,744	£29,163
*Base case							

There are a number of critique points raised by the NICE ERG in relation to the cost effectiveness analyses. There are also considerable limitations in using eosinophilic asthma as a proxy for CEP. The main critique points and limitations are:

- Efficacy data were derived from trials in which reduction in oral corticosteroid was not allowed and so the ICERs are only representative of patients whose dose is not reduced. A reduction in asthma exacerbations was used for the measure of efficacy.
- The benefits of a reduction in oral corticosteroid dose have not been captured in the model which would be expected to lower the ICER for mepolizumab compared to standard of care. However, a reduction in oral corticosteroid use may lead to an increase in asthma exacerbation rates and increase the ICER. It is unclear how these effects would jointly affect the ICER.
- Although there are similarities between eosinophilic asthma and CEP in terms of quality of life, patients with CEP do not experience exacerbations as such, worsening of symptoms would be considered a relapse.
- The preferred measure of response to treatment for CEP patients with mepolizumab is a reduction in oral corticosteroid use, a reduction in exacerbation rate as a proxy for reduction in relapse rate of CEP is a limitation in this model.
- Standard of care treatment for eosinophilic asthma differs from that of CEP
- Clinical experts consider the mortality rate for CEP patients could be similar to that for asthma although the population is considerably smaller and there is not enough evidence to make a confident comparison.

BUDGET IMPACT

In the published studies the mepolizumab regimens varied, particularly by treatment duration. The licensed dose for mepolizumab for treating severe refractory eosinophilic asthma, 100 mg subcutaneously every four weeks, was used with varied treatment length. Medicine and administration costs for mepolizumab regimens and comparators are shown in Table 1. [Confidential information removed]. Clinical experts estimate that 35 people will be eligible for treatment with mepolizumab in Year 1, with seven additional people eligible in each subsequent year. These patients require an alternative treatment option due to corticosteroid induced side effects (after stopping, tapering or while taking corticosteroids). It is assumed

that treatment duration is ongoing with annual review (our timeframe extends to three years); that patients remain on treatment for at least four months (non-responders are then switched), and that efficacy is the same for mepolizumab and comparators (azathioprine and mycophenolate mofetil).

Table 1. Estimated annual acquisition costs in Wales

Regimen/Medicine	Treatment cost (28 days)	Administration cost	Total annual cost per patient	Source
Mepolizumab 100 mg subcutaneously every four weeks ongoing with annual review*	£840	£38	£11,414	BNF costs for mepolizumab. National Schedule of Reference Costs (HRG codes N02AF) for administration[25]
Azathioprine: 200 mg daily†	£4.50	NA	£58.50	BNF costs for azathioprine.
Mycophenolate mofetil: 1 g twice daily ongoing with annual review§	£13.42	NA	£174.43	BNF costs for mycophenolate mofetil.

* using licensed severe refractory eosinophilic asthma adult dose[1]
† Based on 2.5 mg/kg daily and an assumed average patient weight of 76.9 kg[26,27]
§ As per UpToDate [28]
BNF: British National Formulary
BNF costs are exclusive of VAT.

Table 2 shows the estimated annual budget impact in Wales and the net cost over three treatment years. In the scenario used patients have a 50% chance of responding to treatment with either mepolizumab (market with MEP), azathioprine or mycophenolate mofetil (market without MEP). After four months 50% of patients fail treatment and go on to an alternative treatment option (either azathioprine or mycophenolate depending upon their first treatment, but not mepolizumab). The remaining 50% respond to treatment and remain on that treatment long-term (over a three-year timeframe). Clinicians also estimate that the attrition rate for CEP is 10% per year and this has been included in the calculation. An estimated breakdown of eligible patient numbers progressing through mepolizumab treatment at a 50% response rate can be found in Appendix 1.

Table 2. Potential treatment scenario with 50% response rate

	Year 1	Year 2	Year 3
Total number of patients (responders and non-responders) with burn out at 10%	**32**	**37**	**42**
Medicine acquisition costs and administration costs in a market with MEP*	£239,464-240,748	£228,405-230,381	£262,765-264,972
Medicine acquisition costs and administration costs in a market without MEP†	£3,161–4,298	£4144-4474	£4669-5114
Net financial cost	£236,303-236,450	£224,261-225,907	£258,096-259,858

AZA: azathioprine; MEP: mepolizumab; MMF: mycophenolate mofetil
*Patients who are non-responders will receive four months of MEP before switching to either AZA or MMF
†Non-responders (50%) receive four months of AZA and then switch to ongoing MMF or vice versa

Budget impact issues

- In the absence of extensive published data, patient numbers, discontinuation rates (due to either lack of efficacy or burn out) and treatment options have been provided by a clinical expert in Wales.
- It is assumed that efficacy is the same for all three of mepolizumab, azathioprine and mycophenolate mofetil. The efficacy of either azathioprine or mycophenolate mofetil for the treatment of CEP is not supported in the literature.
- Scenario analyses consider people receiving subsequent treatment (after second-line treatment with mepolizumab) with either azathioprine or mycophenolate mofetil although the monitoring and management of adverse effects for these subsequent treatments are not included here and should be factored in to the comparison.
- Adverse event rates have not been included in the budget impact.
- Administration costs were not included for comparators as they are oral medicines while the cost of district nurse time was incorporated into the total cost of mepolizumab.
- Clinicians have indicated that patients would likely remain on mepolizumab long-term with a review of the treatment's efficaciousness taking place annually. Patients could remain on this treatment for many years but a percentage may also experience disease burn out and may be able to wean off treatment.

Welsh commercial access agreement

This medicine is currently not licensed for the indication under consideration (i.e. off-label) and therefore as the Pharmaceutical Industry's code of practice prevents a company from promoting an off-label use of a medicine, a commercial agreement cannot be offered by the company.

ADDITIONAL FACTORS

Prescribing unlicensed medicines

Mepolizumab is not licensed to treat this indication and is therefore 'off-label'. Providers should consult the General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

REFERENCES

1. GlaxoSmithKline. Nucala®. Summary of Product Characteristics. Aug 2019. Available at: https://www.medicines.org.uk/emc/product/1938/smpc#. Accessed Oct 2019.
2. Sarkis E, Patel S, Burns K et al. Anti-interleukin (IL)-5 as a steroid-sparing agent in chronic eosinophilic pneumonia. *Journal of Asthma.* 2018;16:1-5.
3. Lin RY, Santiago TP, and Patel NM. Favorable response to asthma-dosed subcutaneous mepolizumab in eosinophilic pneumonia. *Journal of Asthma.* 2018;65(11):1193-1197.
4. To M, Kono Y, Yamawaki S et al. A case of chronic eosinophilic pneumonia successfully treated with mepolizumab. *The Journal of Allergy and Clinical Immunology. In Practice.* 2018;6(**5**):1746-1747.
5. Suzuki Y, and Suda T. Eosinophilic pneumonia: A review of the previous literature, causes, diagnosis, and management. *Allergology International.* 2019. Available at: .
6. Cottin V, and Cordier JF. Eosinophilic Pneumonias. *Allergy.* 2005;60(7):841-857.
7. Cottin V. Eosinophilic Lung Diseases. *Clinics in Chest Medicine.* 2016;37(3):535-556.
8. Marchand E, and Cordier JF. Idiopathic chronic eosinophilic pneumonia. *Orphanet Journal of Rare Diseases.* 2006;1(11):1-4.
9. Chan C, DeLapp D, and Nystrom P. Chronic eosinophilic pneumonia: Adjunctive therapy with inhaled steroids. *Respiratory Medicine Case Reports.* 2017;22:11-14.
10. Allen J, and Wert M. Eosinophilic Pneumonias. *The Journal of Allergy and Clinical Immunology. In Practice.* 2018;6(5):1455-1461.
11. Yoshida K, Shijubo N, Koba H et al. Chronic eosinophilic pneumonia progressing to lung fibrosis. *The European Respiratory Journal.* 1994;7(8):1541-1544.
12. Sveinsson ÓÁ, Ísaksson HJ, and Guðmundsson G. Chronic eosinophilic pneumonia in Iceland: Clinical features, epidemiology and review. *Laeknabladid.* 2007;93(2):111-116.
13. Suzuki Y, and Suda T. Long-term management and persistent impairment of pulmonary function in chronic eosinophilic pneumonia: A review of the previous literature. *Allergology International.* 2018;67(3):334-340.
14. Crowe M, Robinson D, Sagar M et al. Chronic eosinophilic pneumonia: clinical perspectives. *Therapeutics and Clinical Risk Management.* 2019;15:397-403.
15. Taylor M, and Lin MW. Recurrent eosinophilic pneumonia treated using mepolizumab. Presented at Australasian Society of Clinical Immunology and Allergy. 14-17 Sep 2016.
16. Lam W, and Ramsey A. Novel use of anti-interleukin-5 therapy, mepolizumab, in chronic eosinophilic pneumonia. Presented at Annals of Allergy, Asthma & Immunology. 10-14 Nov 2016.
17. Lawrence R, and Klings ES. Management of chronic eosinophilic pneumonia with mepolizumab. Presented at American Thoracic Society. 17-22 Sep 2019.
18. Jones J, Hostler D, and Hostler J. Beyond steroids: mepolizumab for chronic eosinophilic pneumonia. Presented at Chest Annual Meeting. 19-23 Oct 2019.
19. National Institute for Health and Care Excellence. Technology Appraisal 431. Mepolizumab for treating severe refractory eosinophilic asthma. Jan 2017. Available at: https://www.nice.org.uk/guidance/ta431. Accessed Nov 2019.
20. National Institute for Health and Care Excellence. Mepolizumab for treating severe refractory eosinophilic asthma. Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD) Dec 2016. Available at: https://www.nice.org.uk/guidance/ta431/documents/committee-papers-3. Accessed Nov 2019.
21. Pavord ID, Korn S, and P H. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet.* 2012;380(9842):8.
22. Ortega HG, Liu MC, and ID P. Mepolizumab treatment in patients with severe eosinophilic asthma. *New England Journal of Medicine.* 2014;371:9.

23. Lloyd A, Price D, and R B. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. *Primary Care Respiratory Journal.* 2007;16:5.
24. Lugogo N, Domingo C, and P C. Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: A multi-center, open-label, phase IIIb study. *Clinical Therapeutics.* 2016;38:12.
25. NHS Improvement. National schedule of reference costs. 2017-2018. Available at: https://improvement.nhs.uk/resources/reference-costs/#rc1718. Accessed March 2019.
26. Office for National Statistics. 'Average' Briton highlighted on UN World Statistics Day. Available at: https://www.ons.gov.uk/aboutus/transparencyandgovernance/freedomofinformationfoi/theaveragebriton. Accessed Mar 2019.
27. UpToDate. Azathioprine: Drug information. Available at: https://www.uptodate.com/contents/azathioprine-drug-information?search=azathioprine&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1. Accessed Oct 2019.
28. UpToDate. Treatment and prognosis of interstitial lung disease in systemic sclerosis (scleroderma). Sep 2019. Available at: https://www.uptodate.com/contents/treatment-and-prognosis-of-interstitial-lung-disease-in-systemic-sclerosis-scleroderma#H1942183165. Accessed Oct 2019.

Appendix 1: An estimated breakdown of eligible patient numbers progressing through mepolizumab treatment at a 50% response rate

Patient numbers	Year 1	Year 2	Year 3
Number of people eligible for treatment	35	7	7
Those eligible minus burn out (10%) (rounded value)	32	7	7
New **MEP responders** (50%) (rounded value)	16	4	4
MEP responders carried over from previous year	0	16	19
Previous year's responders minus burn out (10%) (rounded value)	0	15	18
Total number of patients receiving MEP	**16**	**19**	**22**
MEP non-responders carried over from previous year	0	16	18
Previous year's non-responders minus burn out (10%)(rounded value)	0	15	17
Total number of non-responders receiving alternative treatment (AZA or MMF)	**16**	**18**	**20**
Total number of patients (MEP responders and non-responders) minus burn out (10%)	**32**	**37**	**42**
AZA: azathioprine; MEP: mepolizumab; MMF: mycophenolate mofetil			