

Systemic lupus erythematosus: oral mycophenolate

Evidence summary

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[nice.org.uk/guidance/esuom36](https://www.nice.org.uk/guidance/esuom36)

Key points from the evidence

The content of this evidence summary was up-to-date in November 2014. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#), [BNF for children \(BNFc\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

Evidence from a Cochrane review of [randomised controlled trials \(RCTs\)](#) and [quasi-RCTs](#) suggests that mycophenolate mofetil is as effective as cyclophosphamide at inducing remission in lupus nephritis, but with a lower risk of ovarian failure. For maintenance therapy in lupus nephritis the Cochrane review found that mycophenolate mofetil was more effective than azathioprine for preventing relapse, with no increase in clinically important adverse events. Data in non-renal systemic lupus erythematosus mainly come from observational studies; further RCTs assessing the efficacy and safety of mycophenolate in people with non-renal systemic lupus erythematosus are needed.

Regulatory status: Off-label. This topic was prioritised because there was a high volume of requests from the NHS. Immunosuppressants such as mycophenolate are widely used in people with systemic lupus erythematosus, but not all are specifically licensed for this indication.

<p>Effectiveness</p> <ul style="list-style-type: none"> • A Cochrane review found that there was no overall difference for mortality or any renal outcome between mycophenolate mofetil and intravenous (up to 7 studies, n=up to 710) or oral (1 study, n=62) cyclophosphamide for induction therapy in lupus nephritis. • The Cochrane review found that there was a higher risk of renal relapse in people with lupus nephritis maintained on azathioprine compared with those maintained on mycophenolate mofetil (3 studies, n=371, RR 1.83, 95% CI 1.24 to 2.71), but there was no statistically significant difference between them in mortality. • Low quality data in non-renal systemic lupus erythematosus suggest some effectiveness for mycophenolate mofetil. 	<p>Safety</p> <ul style="list-style-type: none"> • Immunosuppressants including mycophenolate have been associated with increased risks of lymphomas, other malignancies, opportunistic infections that can be fatal, sepsis and neutropenia. • Mycophenolate has also been associated with pure red cell aplasia and serious gastrointestinal adverse events (Cellcept, Roche and Myfortic, Novartis summaries of product characteristics).
<p>Patient factors</p> <ul style="list-style-type: none"> • For induction therapy in lupus nephritis, mycophenolate mofetil was found to be associated with a lower risk of toxic adverse events such as ovarian failure, alopecia and leucopenia, compared with cyclophosphamide. • Reduced risk of ovarian failure may be particularly important because systemic lupus erythematosus affects women of child bearing potential. • In a systematic review of mycophenolate mofetil for non-renal manifestations of systemic lupus erythematosus, the most common adverse events were infection (32%), nausea and vomiting (24%) and diarrhoea (12%). 	<p>Resource implications</p> <ul style="list-style-type: none"> • The annual cost of generic mycophenolate mofetil at a dose of 2000 mg to 3000 mg daily is £519.76 to £779.64 (excluding VAT; Drug Tariff, October 2014). • The annual cost of mycophenolate sodium (Myfortic) at a dose of 720 mg twice daily is higher at £2353.40 (excluding VAT; MIMS, October 2014).

Introduction and current guidance

Systemic lupus erythematosus is a chronic autoimmune condition that causes inflammation in the body's tissues. Disease activity varies over time and, at the onset, symptoms are very general and may include unexplained fever, extreme fatigue, muscle and joint pain and skin rash. Active systemic lupus erythematosus involves frequent flares and more severe symptoms compared with inactive disease which is when the disease is in remission. Systemic lupus erythematosus can lead to arthritis, kidney failure, heart and lung inflammation, central nervous system abnormalities and blood disorders.

The aim of current treatments for systemic lupus erythematosus is to control and ease symptoms. Standard therapy includes the use of non-steroidal anti-inflammatory drugs (NSAIDs); corticosteroids such as prednisolone; disease-modifying drugs such as hydroxychloroquine; and immunosuppressants such as azathioprine, cyclophosphamide, methotrexate and mycophenolate mofetil. Rituximab is also considered as a treatment option, particularly in the case of more severe disease, and is covered by an interim [clinical commissioning policy statement](#) by NHS England for certain people with the disease. Not all of these drugs are licensed specifically for use in people with systemic lupus erythematosus and use of some of these drugs would be off-label (see the [summaries of product characteristics](#) for the individual drugs for specific prescribing information). Belimumab is a newer therapy which is licensed for add-on therapy in adults with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity. A NICE technology appraisal, [systemic lupus erythematosus \(autoantibody-positive\) – belimumab](#) is in development (expected date of publication April 2015).

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

Product overview

Mycophenolic acid is an immunosuppressant agent with antiproliferative activity that acts through inhibition of the purine biosynthetic pathway. Mycophenolic acid is available as the prodrug, mycophenolate mofetil (which is available as a generic product or as branded products, such as [Cellcept](#)) or as mycophenolate sodium ([Myfortic](#)).

Both mycophenolate products are licensed for the prophylaxis of acute transplant rejection. Neither is licensed for treating systemic lupus erythematosus, therefore use for this indication is off-label.

NICE has published an evidence summary on another off-label use of mycophenolate: [scleroderma: oral mycophenolate](#) (ESUOM 32).

[Full text of Product overview.](#)

Evidence review

This summary looks at the evidence for using mycophenolate for treating lupus nephritis, and non-renal manifestations of systemic lupus erythematosus. The evidence for lupus nephritis is based on a Cochrane review of RCTs and quasi-RCTs. The evidence for non-renal systemic lupus erythematosus is based mainly on [observational studies](#), but includes 1 RCT which assessed non-renal secondary outcomes in a trial designed primarily to assess the efficacy of mycophenolate in lupus nephritis, and 1 other small RCT. Two small observational studies assessing mycophenolate for juvenile-onset systemic lupus erythematosus are discussed briefly in the evidence summary.

Most of the studies included in this evidence summary used mycophenolate mofetil, rather than mycophenolate sodium, and the dose was normally between 2000 mg and 3000 mg daily. Only 1 study (n=81) in the Cochrane review used mycophenolate sodium for induction therapy in lupus nephritis, and 1 small RCT (n=14) compared mycophenolate sodium with other conventional immunosuppressive agents in people with systemic lupus erythematosus without renal involvement.

- Overall, the Cochrane review ([Henderson et al. 2012](#)) found that there was no difference in mortality or any renal outcome between people receiving mycophenolate mofetil and intravenous or oral cyclophosphamide (off-label use) for induction therapy in lupus nephritis.
 - When mycophenolate mofetil plus corticosteroids was compared with intravenous cyclophosphamide plus corticosteroids there was no statistically significant difference between the groups in mortality (7 studies, n=710, [relative risk](#) [RR] 1.02, 95% [confidence interval](#) [CI] 0.52 to 1.98; absolute risk of mortality in the intravenous cyclophosphamide groups in the studies ranged between 0% and 12%), or complete renal remission (6 studies, n=686, RR 1.39, 95% CI 0.99 to 1.95; absolute rate of complete renal remission in the intravenous cyclophosphamide groups in the studies ranged between 15% and 20%). There was also no statistically significant difference between the groups in partial renal remission (6 studies, n=686), stabilisation of kidney function (5 studies, n=523), incidence of end-stage kidney disease (3 studies, n=231), risk of renal relapse (1 study, n=140), complete remission of proteinuria (6 studies, n=686), partial remission of proteinuria (4 studies, n=602), or daily proteinuria (4 studies, n=271).

- When mycophenolate mofetil plus corticosteroids was compared with oral cyclophosphamide plus corticosteroids, there was also no statistically significant difference between the groups in mortality, incidence of end-stage kidney disease, or other renal outcomes, but all the results were from 1 small study (n=62).
- When mycophenolate mofetil plus corticosteroids was compared with tacrolimus (off-label use) plus corticosteroids, there was no statistically significant difference between them in risk of mortality, end-stage kidney disease, deterioration in kidney function or other renal outcomes. However, these comparisons were based on 1 or 2 small studies (n=40 to 130).
- The combination of mycophenolate mofetil, plus tacrolimus, and corticosteroids was statistically significantly better than intravenous cyclophosphamide plus corticosteroids for increasing the number of people with stable kidney function and complete renal remission. However, these comparisons were based on just 1 small study (n=40).
- Comparing rituximab (off-label use) plus mycophenolate mofetil with mycophenolate mofetil alone found no difference between the groups in risk of mortality, stability of kidney function, or other renal outcomes, but again this was based on 1 small study (n=144).
- Three studies in the Cochrane review ([Henderson et al. 2012](#)) compared azathioprine plus corticosteroids (licensed use) with mycophenolate mofetil plus corticosteroids for maintenance therapy in lupus nephritis (n=371). There was a higher risk of renal relapse in people maintained on azathioprine compared with those on mycophenolate mofetil (RR 1.83, 95% CI 1.24 to 2.71), but there was no statistically significant difference between them in mortality.
- A systematic review ([Pego-Reigosa et al. 2013](#)) assessing the efficacy and safety of non-biologic immunosuppressants in the treatment of non-renal systemic lupus erythematosus in adults included 1 RCT (n=370) and 7 cohort studies (n=584) evaluating mycophenolate mofetil. The primary objective of the included RCT ([Ginzler et al. 2010](#)) was to assess efficacy of mycophenolate in lupus nephritis and the non-renal outcomes were secondary end points with only descriptive analysis. Although the RCT suggests that both mycophenolate mofetil and intravenous cyclophosphamide are effective at treating non-renal manifestations of systemic lupus erythematosus, the results are only applicable to people with lupus nephritis and concurrent non-renal disease activity and may not be generalised to people with systemic lupus erythematosus without renal involvement.

- Another systematic review ([Mok 2007](#)) assessed using mycophenolate mofetil for non-renal manifestations of systemic lupus erythematosus. The review included 20 studies, which were all case series and open-label studies. Favourable results with mycophenolate mofetil were reported in people with haematological disease, while conflicting evidence regarding the efficacy of mycophenolate on lupus skin lesions was reported.
- [Lourdudoss and van Vollenhoven \(2014\)](#) report the results of a single centre retrospective cohort study using mycophenolate mofetil for treating systemic lupus erythematosus and vasculitis. Separate results for those with a diagnosis of systemic lupus erythematosus, and those with vasculitis were not presented and so it is difficult to draw any firm conclusions from this study.
- Two small observational studies ([Falcini et al. \(2009\)](#); n=26, and [Buratti et al \(2001\)](#); n=11) assessed using mycophenolate mofetil for treating juvenile-onset systemic lupus erythematosus. For more information about these studies see the [evidence review section](#).
- The Cochrane review ([Henderson et al. 2012](#)) found that, when used as induction therapy, mycophenolate mofetil was associated with an 85-90% lower risk of ovarian failure, compared with either oral or intravenous cyclophosphamide. The actual risk of ovarian failure ranged from 3% to 4.4% in the intravenous cyclophosphamide groups compared with an estimated risk in the mycophenolate mofetil groups of 0.5% to 0.7%.
 - The incidence of alopecia and leucopenia was also statistically significantly lower with mycophenolate mofetil compared with either oral or intravenous cyclophosphamide. The rate of major infections was statistically significantly lower with mycophenolate mofetil compared with oral cyclophosphamide, but there was no difference compared with intravenous cyclophosphamide.
 - Diarrhoea was statistically significantly more common with mycophenolate mofetil compared with cyclophosphamide, but there was no statistically significant difference in the incidence of vomiting, nausea, or general gastrointestinal upset between groups.
 - There was no difference between mycophenolate mofetil plus corticosteroids and tacrolimus plus corticosteroids in risk of major infection or leucopenia. There was also no difference between rituximab plus mycophenolate mofetil and mycophenolate mofetil alone in risk of major infection or leucopenia.
- The Cochrane review ([Henderson et al. 2012](#)) also reported safety data from studies in maintenance therapy in lupus nephritis. Compared with azathioprine plus corticosteroids, mycophenolate mofetil plus corticosteroids was associated with a statistically significantly lower incidence of leucopenia.

- In the studies assessing mycophenolate for non-renal systemic lupus erythematosus that reported safety, gastrointestinal upset (for example diarrhoea, nausea and vomiting) and infections were the most commonly reported adverse events.
- The evidence base for lupus nephritis comes from a Cochrane review. However the review had some important limitations such as heterogeneity in interventions, definitions of remission and outcome reporting. In addition some of the studies included in the review had follow-up durations that were too short to pick up important outcomes such as remission with cyclophosphamide, ovarian failure and end-stage kidney disease. The evidence base for non-renal manifestations of systemic lupus erythematosus is mainly based on observational studies, which have limitations inherent in their non-randomised design. Of the 2 RCTs included, 1 assessed non-renal secondary outcomes in a trial primarily designed to assess efficacy in lupus nephritis; therefore limiting the applicability of the results to people with systemic lupus erythematosus without renal involvement. The other RCT was very small (n=14) and underpowered.

Context and estimated impact for the NHS

The estimated annual cost of generic mycophenolate mofetil at a dose of 2000 mg to 3000 mg daily is £519.76 to £779.64 ([Drug Tariff](#) October 2014; excluding VAT). Mycophenolate sodium (Myfortic) is more expensive, at an estimated annual cost of £2353.40 for 720 mg twice daily ([MIMS](#) October 2014; excluding VAT).

No estimate of the current use of off-label mycophenolate for treating systemic lupus erythematosus in UK clinical practice was identified.

[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 systemic lupus erythematosus who are thinking about trying mycophenolate.

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

Systemic lupus erythematosus is a chronic autoimmune condition that causes inflammation in the body's tissues. It affects the whole body including the skin, joints, internal organs and serous membranes and results in chronic debilitating ill health. The cause of systemic lupus erythematosus is unknown though a combination of genetic, environmental and hormonal factors is thought to play a role in disease development and progression. Disease activity varies over time and, at the onset, symptoms are very general and may include unexplained fever, extreme fatigue, muscle and joint pain and skin rash. Active systemic lupus erythematosus involves frequent flares and more severe symptoms compared with inactive disease which is when the disease is in remission. Systemic lupus erythematosus can lead to arthritis, kidney failure, heart and lung inflammation, central nervous system abnormalities and blood disorders. Over 90% of people with systemic lupus erythematosus develop problems with their joints and muscles such as arthralgia (joint pain) and myalgia (muscle pain). Renal disease also occurs in 40 to 75% of people with systemic lupus erythematosus and significantly contributes to morbidity and mortality. Long-term damage accrues as a result of persistent disease activity and also due to cumulative effects of steroids.

The prevalence of systemic lupus erythematosus is significantly higher in African-Caribbean, South Asian and Chinese populations compared with European white populations. Although the severity of the disease is greater in the male population, systemic lupus erythematosus is significantly more common in women (90%) than men (10%) and mainly affects people aged 15-60 years old.

The aim of current treatments for systemic lupus erythematosus is to control and ease symptoms. Standard therapy includes the use of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids such as prednisolone, disease-modifying drugs such as hydroxychloroquine and immunosuppressants such as azathioprine, cyclophosphamide, methotrexate, and mycophenolate mofetil. Rituximab is also considered as a treatment option, particularly in the case of more severe disease, and is covered by an interim [clinical commissioning policy statement](#) by NHS England for certain people with the disease. Not all of these drugs are licensed specifically for use in people with systemic lupus erythematosus and use of some of these drugs would be off-label (see the [summaries of product characteristics](#) for the individual drugs for specific prescribing information). See [systemic lupus erythematosus \(active\) – belimumab](#) final scope for further information on this condition.

Belimumab is a newer therapy which is licensed for add-on therapy in adults with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity. A NICE technology appraisal, [systemic lupus erythematosus \(autoantibody-positive\) – belimumab](#) is in development (expected date of publication April 2015).

Evidence-based recommendations on the management of systemic lupus erythematosus, were published by The European League Against Rheumatism (EULAR) task force for systemic lupus erythematosus in 2008 ([Bertsias et al. 2008](#)); and on the management of adult and paediatric lupus nephritis by the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) in 2012 ([Bertsias et al. 2012](#)) The American College of Rheumatology published a guideline on screening, treatment and management of lupus nephritis in 2012 ([Hahn et al. 2012](#)). The [British Society for Rheumatology](#) is also developing a guideline for systematic lupus erythematosus management.

Product overview

Drug action

Mycophenolic acid is an immunosuppressant agent with antiproliferative activity that acts through inhibition of the purine biosynthetic pathway. Mycophenolic acid is available as the prodrug, mycophenolate mofetil (which is available as a generic product or as branded products, such as [Cellcept](#)) or as mycophenolate sodium ([Myfortic](#)).

The summary of product characteristics for mycophenolate sodium ([Myfortic](#)) states that mycophenolic acid (as sodium salt) and mycophenolate mofetil should not be indiscriminately interchanged or substituted because of their different pharmacokinetic profiles.

Regulatory status

Mycophenolate mofetil ([Cellcept](#), Roche) is licensed in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in people receiving allogeneic renal, cardiac or hepatic transplants. Mycophenolate sodium ([Myfortic](#), Novartis) is licensed in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adults receiving allogeneic renal transplants.

Neither mycophenolate product is licensed for treating systemic lupus erythematosus, therefore using mycophenolate mofetil or mycophenolate sodium for this indication is off-label.

NICE has published an evidence summary on another off-label use of mycophenolate: [scleroderma: oral mycophenolate](#) (ESUOM 32).

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 mycophenolate mofetil outside its authorised indications.

Cost

The [Drug Tariff](#) (October 2014) lists the following cost for mycophenolate mofetil; excluding VAT:

- 50×mycophenolate mofetil 500 mg tablets = £17.80

[MIMS](#) (October 2014) lists the following costs for the branded products, Cellcept (mycophenolate mofetil) and Myfortic (mycophenolate sodium); excluding VAT and any locally or nationally negotiated procurement discounts:

- 100×Cellcept 250 mg capsules = £82.26
- 50×Cellcept 500 mg tablets = £82.26
- 120×Myfortic 180 mg tablets = £96.72
- 120×Myfortic 360 mg tablets = £193.43

Evidence review

Clinical effectiveness

Mycophenolate for lupus nephritis

A Cochrane review has assessed the efficacy and safety of various immunosuppressants, including mycophenolate, for induction and maintenance therapy in lupus nephritis ([Henderson et al. 2012](#)). This review updates a previous review from 2004 which concluded that cyclophosphamide combined with corticosteroids was the preferred treatment option to preserve kidney function in people with proliferative lupus nephritis ([Flanc et al. 2004](#)). Since the publication of the 2004 review, a number of trials investigating the effect of newer therapies on lupus nephritis, such as tacrolimus, mycophenolate mofetil and rituximab, have been published.

The 2012 Cochrane review ([Henderson et al. 2012](#)) included a total of 50 (n=2846) randomised controlled trials (RCTs), and quasi-RCTs in children, young people and adults with biopsy-proven lupus nephritis. Several drugs were investigated in the studies including mycophenolate, cyclophosphamide, corticosteroids, tacrolimus, rituximab, azathioprine, ciclosporin and intravenous immunoglobulin. Most of the included studies examined the effects of treatment for induction therapy for lupus nephritis, rather than maintenance treatment.

The following studies of mycophenolate for induction therapy in lupus nephritis were included:

- 8 studies (n=786) comparing mycophenolate mofetil plus corticosteroids with cyclophosphamide plus corticosteroids.
- 1 study (n=40) comparing mycophenolate mofetil plus tacrolimus plus corticosteroids with cyclophosphamide plus corticosteroids.
- 2 studies (n=149) comparing mycophenolate mofetil plus corticosteroids with tacrolimus plus corticosteroids.
- 1 study (n=81) comparing standard dose corticosteroids with reduced dose corticosteroids with both arms receiving mycophenolate sodium.
- 1 study (n=144) comparing rituximab plus mycophenolate mofetil plus corticosteroids with mycophenolate mofetil plus corticosteroids.

The review also included 2 studies comparing mycophenolate mofetil plus corticosteroids with azathioprine plus corticosteroids (n=332), and 1 study comparing mycophenolate mofetil plus

corticosteroids with azathioprine or intravenous cyclophosphamide plus corticosteroids (n=59), for maintenance therapy in lupus nephritis.

All studies included corticosteroids but the regimens used varied.

Most of the included studies used mycophenolate mofetil at a dosage of 2000–3000 mg per day. One study used mycophenolate sodium at a target dosage of 2160 mg per day. Follow-up ranged from 6 to 12 months for induction therapy and 12 to 72 months for maintenance therapy.

Induction therapy

Overall, the Cochrane review ([Henderson et al. 2012](#)) found that there was no difference in mortality or any renal outcome between people receiving mycophenolate mofetil and intravenous (or oral cyclophosphamide (off-label use) for induction therapy in lupus nephritis:

- When mycophenolate mofetil plus corticosteroids was compared with intravenous cyclophosphamide plus corticosteroids there was no statistically significant difference between the groups in mortality (7 studies, n=710, [relative risk \[RR\]](#) 1.02, 95% [confidence interval \[CI\]](#) 0.52 to 1.98; absolute risk of mortality in the intravenous cyclophosphamide groups in the studies ranged between 0% and 12%). There was also no statistically significant difference between the groups in complete renal remission (6 studies, n=686, RR 1.39, 95% CI 0.99 to 1.95; absolute rate of complete renal remission in the intravenous cyclophosphamide groups in the studies ranged between 15% and 20%), partial renal remission (6 studies, n=686, RR 1.04, 95% CI 0.86 to 1.25), stabilisation of kidney function (5 studies, n=523, RR 1.05, 95% CI 0.94 to 1.18), incidence of end-stage kidney disease (3 studies, n=231, RR 0.71, 95% CI 0.27 to 1.84), risk of renal relapse (1 study, n=140, RR 0.97, 95% CI 0.39 to 2.44), complete remission of proteinuria (6 studies, n=686, RR 1.16, 95% CI 0.85 to 1.58), partial remission of proteinuria (4 studies, n=602, RR 1.06, 95% CI 0.89 to 1.25), or daily proteinuria (4 studies, n=271, RR -0.11, 95% CI -0.64 to 0.42).
- When mycophenolate mofetil plus corticosteroids was compared with oral cyclophosphamide plus corticosteroids, there was also no statistically significant difference between the groups in mortality (1 study, n=62, RR 0.19, 95% CI 0.01 to 3.76), incidence of end-stage kidney disease (1 study, n=62, RR 0.19, 95% CI 0.01 to 3.76), or other renal outcomes, but all the results were from 1 small study.

When mycophenolate mofetil plus corticosteroids was compared with tacrolimus plus corticosteroids (off-label use), there was no statistically significant difference between them in risk of mortality (2 studies, n=130, RR 1.87, 95% CI 0.34 to 10.44), end-stage kidney disease,

deterioration in kidney function, or other renal outcomes. However, these comparisons were based on 1 or 2 small studies (n=40 to 130).

The combination of mycophenolate mofetil plus tacrolimus and corticosteroids was statistically significantly better than intravenous cyclophosphamide plus corticosteroids for increasing the number of people with stable kidney function (1 study, n=40, RR 1.73, 95% CI 1.15 to 2.60), complete renal remission (1 study, n=40, RR 4.33, 95% CI 1.45 to 12.91) and complete remission in proteinuria (1 study, n=40, RR 4.33, 95% CI 1.45 to 12.91). Daily proteinuria was also statistically significantly lower for people treated with mycophenolate mofetil plus tacrolimus. However, these comparisons were based on just 1 small study (n=40).

Comparing rituximab (off-label use) plus mycophenolate mofetil with mycophenolate mofetil alone found no difference between the groups in risk of mortality, stability of kidney function, or other renal outcomes, but again this was based on 1 small study (n=144).

The 1 study (n=81) in the Cochrane review that assessed using mycophenolate sodium (as opposed to mycophenolate mofetil) for induction therapy in lupus nephritis, compared standard dose corticosteroids plus mycophenolate sodium with reduced dose corticosteroids plus mycophenolate sodium. No difference was found between the groups in complete or partial renal remission.

Maintenance therapy

In the comparison of azathioprine plus corticosteroids (licensed use) with mycophenolate mofetil plus corticosteroids for maintenance therapy in lupus nephritis, there was a higher risk of renal relapse in people maintained on azathioprine compared with those on mycophenolate mofetil (3 studies, n=371, RR 1.83, 95% CI 1.24 to 2.71). However, there was no statistically significant difference between azathioprine and mycophenolate mofetil in mortality (3 studies, n=371, RR 0.58, 95% CI 0.10 to 3.49), end-stage kidney disease (3 studies, n=371, RR 1.86, 95% CI 0.37 to 9.31) or doubling of serum creatinine (3 studies, n=371, RR 2.09, 95% CI 0.89 to 4.94).

Mycophenolate for non-renal manifestations of systemic lupus erythematosus

A systematic review ([Pego-Reigosa et al. 2013](#)) assessed the efficacy and safety of non-biologic immunosuppressants in the treatment of non-renal systemic lupus erythematosus in adults. The review included 8 studies (1 RCT [n=370] and 7 cohort studies [n=5849]) evaluating mycophenolate mofetil. Pego-Reigosa et al. discuss that although the evidence for use of mycophenolate mofetil in non-renal systemic lupus erythematosus is based on studies of a reasonably large number of patients, the included studies were often low quality. They conclude

that further RCTs assessing the efficacy and safety of mycophenolate as a primary endpoint in people with non-renal systemic lupus erythematosus are needed.

The RCT included in the [Pego-Reigosa et al. \(2013\)](#) review ([Ginzler et al. 2010](#)), explored the non-renal secondary endpoints included in the [ALMS study](#), which was a 24-week randomised, open-label parallel-group clinical trial that was designed to compare the effects of mycophenolate mofetil (target dose 3000 mg per day) with intravenous cyclophosphamide for induction treatment in 370 people with lupus nephritis. The ALMS study is included in the Cochrane review ([Henderson et al. 2012](#)) above which assessed the efficacy and safety of various immunosuppressants, for induction and maintenance therapy in lupus nephritis.

Non-renal secondary end points included measures of disease activity assessed by the [British Isles Lupus Assessment Group \(BILAG\) disease activity index](#), and the [Safety of Estrogens in Lupus Erythematosus: National Assessment \(SELENA\) version of the Systemic Lupus Erythematosus Disease Activity Index \(SLEDAI\)](#). The BILAG disease activity index consists of 86 items for recording lupus disease activity across 8 organs or systems: general, mucocutaneous, central nervous system, musculoskeletal, renal, cardiovascular/respiratory, vasculitis and haematological. Disease activity is categorised from grade A (very active disease, usually needing treatment with prednisolone doses of more than 20 mg daily or immunosuppressants) to grade E (no current or previous disease activity in that system). The SELENA version of the SLEDAI is a sum of 24 criteria for 9 organ systems and categorises disease activity as high (score of more than 6), low (score of more than 2 to 6) and normal (score of 2 or less). It also identifies mild or moderate (increase in score of 3 or more from baseline and a total score of less than 12) and severe (increase in score of 12 or more from baseline) disease flares. Non-renal data from the SELENA-SLEDAI was calculated by excluding renal parameters from the score.

At week 24 (or the end point using last observation carried forward), [Ginzler et al. 2010](#) report that similar proportions of people in the mycophenolate mofetil and intravenous cyclophosphamide groups with a grade A or B score on the BILAG index at baseline, achieved a grade D or grade C or D in all disease domains (with the exception of the renal domain where slightly more people on mycophenolate mofetil compared with intravenous cyclophosphamide showed a reduction in disease activity from baseline). At week 24, non-renal SELENA-SLEDAI scores improved (reduced) in both treatment groups from baseline (score change: -3.3 ± 4.5 points at week 24 from a baseline of 5.8 ± 4.7 points in the mycophenolate mofetil group; and -3.9 ± 4.9 points at week 24 from a baseline of 6.6 ± 4.8 in the intravenous cyclophosphamide group). Ginzler et al conclude that both mycophenolate mofetil and intravenous cyclophosphamide are effective at treating non-renal manifestations in people with lupus nephritis. However they caution that the results are only

applicable to people with lupus nephritis and concurrent non-renal disease activity and may not be generalised to people with systemic lupus erythematosus without renal involvement.

Another systematic review ([Mok 2007](#)) assessed using mycophenolate mofetil for non-renal manifestations of systemic lupus erythematosus. The review included 20 studies, which were all case series and open-label studies. Most of the included studies used dosages of 2000-3000 mg of mycophenolate mofetil daily.

The main indications for mycophenolate mofetil were refractory haematological (10 people) and dermatological (16 people) manifestations of systemic lupus erythematosus. The authors state that a good response to mycophenolate mofetil was generally reported in all 10 people with haematological disease. Conflicting evidence regarding the efficacy of mycophenolate mofetil on lupus skin lesions was reported; 11/16 (69%) people described some response (improvement or definite improvement of symptoms, remission, partial response or initial response only), whereas the remaining 5/16 (31%) people, reported no response to mycophenolate mofetil. The efficacy of mycophenolate mofetil in neuropsychiatric lupus was difficult to ascertain because most people were taking concomitant medications such as corticosteroids, or intravenous immunoglobulins and the effect of mycophenolate mofetil could not be separated from that of these other medicines

One 16-week, open-label RCT ([Yahya et al. 2013](#)) assessed the efficacy of mycophenolate sodium 720 mg twice daily (n=8) compared with other conventional immunosuppressive agents (azathioprine or dapsone; n=6) in people with active systemic lupus erythematosus without renal involvement.

SLEDAI scores (the primary outcome) improved in 7/8 people in the mycophenolate sodium group, and 4/6 people in the control group. There was no statistically significant difference between the groups. However, the small number of people included in this study means it was underpowered and limits any conclusions that can be drawn.

[Lourdudoss and van Vollenhoven et al. \(2014\)](#) report the results of a single centre retrospective cohort study (n=178) using mycophenolate mofetil for treating systemic lupus erythematosus and systemic vasculitis. The cohort included 135 people with systemic lupus erythematosus treated with mycophenolate mofetil up to a target dose of 2000 mg daily. At 12-months follow-up, 46% of all participants (systemic lupus erythematosus and systemic vasculitis) were described as having a good response to mycophenolate mofetil, 13% had a partial response but had been switched to a different therapy by their clinician, 31% had no response, and data was missing for 10% of participants. Separate results for those with a diagnosis of systemic lupus erythematosus and those with systemic vasculitis were not presented and so it is difficult to draw any firm conclusions from

this study. However, mycophenolate mofetil was associated with a statistically significant reduction in concomitant corticosteroid dose in all participants from a mean prednisolone dose 21.7 mg daily at baseline, to 8.3 mg daily after 12 months ($p < 0.05$).

Mycophenolate for juvenile onset systemic lupus erythematosus

Falcini et al. (2009) report a retrospective cohort study in 26 children and young people with juvenile onset systemic lupus erythematosus (mean age at diagnosis 12.7 years) who received mycophenolate mofetil (mean age on starting mycophenolate mofetil 15.9 years).

Overall, mycophenolate mofetil reduced disease activity, or was successful as a steroid-sparing agent in 14 participants (54%), stabilised the disease in 8 participants (31%) and was ineffective in 4 participants (15%). A total of 23 participants completed at least 12 months of follow-up, and in these participants there was a statistically significant improvement in SLEDAI score from baseline (figures reported graphically, $p < 0.05$).

Buratti et al (2001) report a cohort study in 11 children and young people with juvenile onset systemic lupus erythematosus (mean age at disease onset 12.3 years) who received mycophenolate mofetil 17–42 mg/kg/day in 2 divided doses, or 1250–2250 mg daily for severe renal disease. The mean duration of therapy was 9.8 months. All participants received concomitant prednisolone, and 7/11 were taking hydroxychloroquine.

Mean SLEDAI score improved in 80% of participants from 9.6 at baseline to 3.4 after a mean of 10 months treatment. A total of 4 participants were reported as having an overall excellent response to mycophenolate mofetil. Concomitant prednisolone was discontinued in 1 participant, reduced in 9 and remained unchanged in 1.

Safety and tolerability

The Cochrane review (Henderson et al. 2012) assessed the efficacy and safety of various immunosuppressants, including mycophenolate, for induction and maintenance therapy in lupus nephritis.

When used as induction therapy, mycophenolate mofetil was associated with an 85% to 90% lower risk of ovarian failure, compared with either oral (1 study, $n=53$, RR 0.10, 95% CI 0.01 to 0.73) or intravenous (2 studies, $n=498$, RR 0.15, 95% CI 0.03 to 0.80) cyclophosphamide. The actual risk of ovarian failure ranged from 3% to 4.4% in the intravenous cyclophosphamide groups, compared with an estimated risk in the mycophenolate mofetil groups of 0.5% to 0.7%. This finding may be

particularly important in systemic lupus erythematosus because it is a condition that is significantly more common in women than men and mainly affects people aged 15-60 years old, which includes women of child bearing potential.

The incidence of alopecia and leucopenia was also statistically significantly lower with mycophenolate mofetil compared with either oral or intravenous cyclophosphamide. The rate of major infections was statistically significantly lower with mycophenolate mofetil compared with oral cyclophosphamide, but there was no difference compared with intravenous cyclophosphamide. No difference in herpes zoster virus infection was seen with mycophenolate mofetil compared with either oral or intravenous cyclophosphamide.

Diarrhoea was statistically significantly more common with mycophenolate mofetil compared with cyclophosphamide (3 studies, n=569, RR 2.53, 95% CI 1.54 to 4.16; actual risk of diarrhoea in the intravenous cyclophosphamide group 2.7% to 12.8%, estimated risk of diarrhoea in the mycophenolate mofetil group 6.8% to 32.4%), but there was no statistically significant difference in the incidence of vomiting, nausea, or general gastrointestinal upset between groups.

Malignancy was only reported in 1 study, and there was no difference between mycophenolate mofetil and cyclophosphamide (1 study, n=364, RR 0.65, 95% CI 0.11 to 3.86).

When mycophenolate mofetil plus corticosteroids was compared with tacrolimus plus corticosteroids for induction therapy in lupus nephritis there was no statistically significant difference between them in risk of major infection or leucopenia.

In the 1 study that compared rituximab plus mycophenolate mofetil with mycophenolate mofetil alone for induction therapy in lupus nephritis, there was no difference between the groups in risk of major infection or leucopenia.

The Cochrane review also reported data from studies in maintenance therapy in lupus nephritis. Compared with azathioprine plus corticosteroids, mycophenolate mofetil plus corticosteroids was associated with a statistically significantly lower incidence of leucopenia (2 studies, n=331, RR comparing azathioprine plus corticosteroids with mycophenolate mofetil plus corticosteroids 6.21, 95% CI 1.69 to 22.85).

The systematic review by [Mok 2007](#) assessed using mycophenolate mofetil for non-renal manifestations of systemic lupus erythematosus. However, because of the limited number of people receiving treatment with mycophenolate mofetil for non-renal indications, the authors pooled safety data from uncontrolled series, and randomised trials in people with lupus nephritis.

The most common adverse events associated with mycophenolate mofetil were infection (77/241 [32%]), nausea and vomiting (59/241 [24%]), and diarrhoea (28/241 [12%]). Despite the high rate of infections, most of these were minor, and only 2% of infections were classed as serious.

A small study (n=14) by [Yahya et al. 2013](#) assessed the efficacy and safety of mycophenolate sodium (as opposed to mycophenolate mofetil) compared with other conventional immunosuppressive agents in people with active systemic lupus erythematosus without renal involvement. One person experienced diarrhoea and vomiting while taking mycophenolate sodium 720 mg twice daily. However this improved when the dose was changed to 360 mg taken 4 times daily. No other adverse events were reported.

[Lourdudoss and van Vollenhoven \(2014\)](#) report safety data from a single centre retrospective cohort study (n=178) using mycophenolate mofetil for treating systemic lupus erythematosus and systemic vasculitis. After 1 month of follow-up, adverse events were reported by 33% of people, of whom 26% discontinued treatment because of the adverse event. After 12 months of follow-up, 14% of people had experienced a mild adverse event, and 6% had experienced a moderate adverse event. Treatment was discontinued due to adverse events in 16% of people. The most common adverse events leading to discontinuation were gastrointestinal (40%) and general adverse events such as fatigue pain and headache (30%).

[Falcini et al. \(2009\)](#) and [Buratti et al \(2001\)](#) report the safety and efficacy of mycophenolate mofetil in juvenile onset systemic lupus erythematosus. Falcini et al. report that 3/26 (11.5%) participants discontinued mycophenolate mofetil due to minor adverse events and 2 participants experienced severe chronic diarrhoea. Buratti et al. report that mycophenolate mofetil was overall well tolerated. One participant discontinued treatment due to an adverse event. The most commonly reported adverse events were infections in 4/11 (36%) participants, and nausea in 4/11 (36%) participants.

The summaries of product characteristics (SPCs) for mycophenolate mofetil ([Cellcept](#), Roche) and mycophenolate sodium ([Myfortic](#), Novartis) state that people receiving immunosuppressive regimens involving combinations of medicines that include mycophenolate, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. They also state that people receiving immunosuppressants, including mycophenolate, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis. The SPCs advise that people taking mycophenolate should report immediately any evidence of infection, unexpected bruising, bleeding or anything else that indicates bone marrow depression.

The SPCs advise that people taking mycophenolate should be monitored for neutropenia, and have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. They also state that because mycophenolate has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, haemorrhage and perforation, it should be used with caution in people with active serious digestive system disease. People should also be advised that during treatment with mycophenolate, vaccinations may be less effective, and the use of live attenuated vaccines should be avoided.

The SPCs recommend that mycophenolate should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning mycophenolate therapy, during therapy, and for 6 weeks following discontinuation of therapy.

In the [July 2009 edition of Drug Safety Update](#), the Medicines and Healthcare products Regulatory Agency (MHRA) warned about the risk of pure red cell aplasia with mycophenolate mofetil. The MHRA advised that mycophenolate mofetil should be discontinued or the dose reduced in people who develop pure red cell aplasia.

Evidence strengths and limitations

The evidence base for mycophenolate for the treatment of lupus nephritis in this evidence summary comes from a Cochrane review ([Henderson et al. 2012](#)). The review had important strengths; it organised interventions into those used in induction and those used in maintenance and so more accurately reflects clinical practice. In addition the review included both published and unpublished data (from conference abstracts), which may reduce the risk of publication bias. The review only included RCTs and quasi RCTs, which also strengthens the quality of the included evidence. However, the review had some important limitations; there was considerable clinical heterogeneity in interventions (for example dosage, route of administration and concomitant interventions), definitions of remission and outcome reporting. Some of the studies had follow-up durations that were too short to pick up important outcomes such as remission, ovarian failure, end-stage kidney disease and malignancies. Incomplete recording of outcomes also limits the findings.

The evidence for mycophenolate for treating non-renal manifestations of systemic lupus erythematosus was mainly based on observational studies, which have limitations inherent in their non-randomised design.

A systematic review by [Pego-Reigosa et al. 2013](#) aimed to assess the efficacy and safety of non-biologic immunosuppressants in the treatment of non-renal systemic lupus erythematosus in adults. The review included 7 cohort studies and 1 RCT ([Ginzler et al. 2010](#)) evaluating mycophenolate mofetil. The RCT suggests that both mycophenolate mofetil and intravenous cyclophosphamide are effective at treating non-renal manifestations in people with lupus nephritis as measured using validated scoring systems including the BILAG disease activity index, and the SELENA-SLEDAI. However Ginzler et al caution that the results are only applicable to people with lupus nephritis and concurrent non-renal disease activity and may not be generalised to people with systemic lupus erythematosus without renal involvement. In addition, the non-renal endpoints reported in this RCT were secondary endpoints with descriptive analyses only, and the trial was not powered to detect differences for these.

The only other RCT ([Yahya et al. 2013](#)) included in this evidence summary assessing the efficacy of mycophenolate in people with systemic lupus erythematosus without renal involvement compared mycophenolate sodium (as opposed to mycophenolate mofetil) with other conventional immunosuppressive agents. This trial was very small (n=14) and significantly underpowered to detect differences between the 2 groups.

Another study included in the evidence summary was [Lourdudoss and van Vollenhoven \(2014\)](#). This study was a single centre retrospective cohort study reporting the use of mycophenolate mofetil for treating systemic lupus erythematosus and systemic vasculitis. The study was observational in nature, and in addition reported combined results for both people with systemic vasculitis and people with systemic lupus erythematosus. Information on using mycophenolate for treating systemic lupus erythematosus only could not be taken from the study. However, the study did suggest a statistically significant steroid sparing effect with mycophenolate mofetil in all participants, which could be clinically significant for people with systemic lupus erythematosus.

Two studies looked at using mycophenolate mofetil for juvenile onset systemic lupus erythematosus, [Falcini et al. \(2009\)](#) and [Buratti et al \(2001\)](#). The small number of participants included in these studies (n=26 and n=11 respectively) and the observational nature of the studies limits the conclusions that can be drawn from them.

Most of the evidence in this evidence summary relates to mycophenolate mofetil. Only 1 study (n=81) in the Cochrane review used mycophenolate sodium in induction therapy in lupus nephritis, and 1 small RCT (n=14) compared mycophenolate sodium with other conventional immunosuppressive agents in people with systemic lupus erythematosus without renal involvement. This limits the conclusions that can be drawn about using mycophenolate sodium in lupus nephritis, and non-renal manifestations of systemic lupus erythematosus.

Context and estimated impact for the NHS

Cost effectiveness

The aim of current treatments for systemic lupus erythematosus is to control and ease symptoms. Standard therapy includes the use of NSAIDs, corticosteroids such as prednisolone, disease-modifying drugs such as hydroxychloroquine and immunosuppressants such as azathioprine, cyclophosphamide, methotrexate, and mycophenolate mofetil. Rituximab is also considered as a treatment option, particularly in the case of more severe disease. Belimumab, a newer therapy which is licensed for add-on therapy in adults with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity despite standard therapy is being covered by a [NICE technology appraisal](#). See [the introduction section](#) for more details.

	Usual dose ^a	Estimated annual cost ^b
Oral azathioprine	1–3 mg/kg daily	Based on a 75 kg adult: £74.04 to £143.26 ^c
Oral cyclophosphamide	2.5 mg/kg daily	Based on a 75 kg adult: £897.90 ^{c,d}
Intravenous cyclophosphamide	0.5-1 g/m ² body surface area monthly	Based on a body surface area of 1.79m ² : £204.72 to £409.44 ^e
Oral methotrexate	7.5–25 mg once weekly	£14.49 to £48.29 ^c
Subcutaneous methotrexate	7.5–25 mg once weekly	£772.20 to £960.96 ^f
Oral mycophenolate mofetil	2000-3000 mg daily in 2 divided doses	£519.76 to £779.64 ^c
Oral mycophenolate sodium	1440 mg daily in 2 divided doses	£2353.40 ^f
Intravenous rituximab	1000 mg on day 1, and 15 ^g	£3492.60 ^f
Oral tacrolimus	0.06 to 0.1 mg/kg daily in 2 divided doses	Based on a 75 kg adult: £1939.18 to £3158.57 ^{f,h}

^a Doses based on those used in the [Henderson et al. 2012](#) Cochrane review, or taken from the [summaries of product characteristics](#) for other indications. Not all of these drugs are licensed specifically for use in people with systemic lupus erythematosus and use of some of these drugs would be off-label (see the [summaries of product characteristics](#) for the individual drugs for specific prescribing information). The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.

^b Costs are given excluding VAT and do not take into account any local or national procurement discounts.

^c Costs taken from the [Drug Tariff](#), October 2014.

^d The only strength tablet available is 50 mg, therefore dose rounded down to nearest multiple of 50 mg.

^e Costs taken from the [BNF](#), October 2014, and assume vial wastage.

^f Costs taken from [MIMS](#), October 2014.

^g Dose as recommended in the NHS England Interim Clinical Commissioning Policy Statement: [Rituximab for the treatment of Systemic Lupus Erythematosus in adults](#).

^h Costs based on Adoport brand of tacrolimus. Costs may vary depending on the brand prescribed. In the [June 2012 edition of Drug Safety Update](#), the MHRA warned that oral tacrolimus products should be prescribed and dispensed by brand name only, to minimise the risk of inadvertent switching between products, which has been associated with reports of toxicity and graft rejection.

Current drug usage

No estimate of the current use of off-label mycophenolate for the treatment of systemic lupus erythematosus in UK clinical practice was identified.

In the year from April 2013 to March 2014, 182,606 prescriptions for mycophenolate mofetil that were prescribed in primary care in England were dispensed at a net cost of just under £10 million. For mycophenolate sodium, the figure was 14,779 prescriptions at a net cost of just under £2 million. It is not known how many of these prescription items were for systemic lupus erythematosus (personal communication: [NHS Business Services Authority](#), May 2014).

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 systemic lupus erythematosus who are thinking about trying mycophenolate.

Relevance to NICE guidance programmes

There is currently no NICE guidance on the treatment of systemic lupus erythematosus. A NICE technology appraisal, [systemic lupus erythematosus \(autoantibody-positive\) – belimumab](#) is in development (expected date of publication April 2015). The technology appraisal will not be considering belimumab for treating severe active lupus nephritis or severe active central nervous system lupus in line with the marketing authorisation for the drug.

NICE has issued guidance that includes recommendations for licensed indications of mycophenolate mofetil:

- [Immunosuppressive therapy for renal transplantation in adults](#) (2004) NICE technology appraisal guidance 85
- [Immunosuppressive therapy for renal transplantation in children and adolescents](#) (2006) NICE technology appraisal 99

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Development of this evidence summary

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

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Declarations of interest

Caroline Gordon has acted as a consultant providing advice on design and analysis of lupus clinical trials to various pharmaceutical companies. Caroline Gordon has received honoraria for lecturing and support for attending meetings from various pharmaceutical companies. Caroline Gordon has received an unrestricted educational grant from Aspreva Pharmaceuticals/Vifor Pharma UK limited.

Ian Bruce has received honoraria for an advisory board and speaker fees from Aspreva Pharmaceuticals/Vifor Pharma UK limited.

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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