NICE National Institute for Health and Care Excellence

NICE guidance

Lesinurad for treating chronic hyperuricaemia in people with gout

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

1.1 Lesinurad is not recommended within its marketing authorisation, that is, with a xanthine oxidase inhibitor for treating hyperuricaemia in adults with gout whose serum uric acid is above the target level despite an adequate dose of a xanthine oxidase inhibitor alone.

1.2 This recommendation is not intended to affect treatment with lesinurad that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made this recommendation

Drug treatments for gout include 2 xanthine oxidase inhibitors, allopurinol or, if that is not tolerated, febuxostat. Evidence from 2 randomised controlled trials shows that more people on lesinurad plus allopurinol reach a target serum uric acid level than people on allopurinol alone. This outcome is seen as clinically relevant when treating gout, but the number of flares and tophi healing are more important outcomes for patients. It is plausible that lowering serum uric acid levels reduces the number of flares and improves healing of tophi, but the clinical evidence does not show that lesinurad plus allopurinol improves these outcomes compared with allopurinol alone.

The main factors affecting the cost effectiveness of lesinurad are the assumptions that lowering serum uric acid levels in people with gout improves quality of life and that it prolongs life. Results from observational studies suggest that people with chronic gout have a shorter life expectancy than people without gout. However, there is no robust evidence from randomised trials to show that lowering serum uric acid levels extends life.

The preferred cost-effectiveness estimate for lesinurad plus allopurinol compared with allopurinol alone is £62,298 per quality-adjusted life year gained. However, this estimate is not based on comparing lesinurad plus allopurinol with the highest possible dose of allopurinol, so the most plausible cost-effectiveness estimate could be even higher. Because this is substantially above the range normally considered by NICE to be a cost-effective use of NHS resources, lesinurad cannot be recommended.

2 Information about lesinurad

Marketing authorisation	Lesinurad (Zurampic, Grünenthal) taken with a xanthine oxidase inhibitor has a marketing authorisation for treating hyperuricaemia in adults with gout, with or without tophi, whose serum uric acid is above the target level with an adequate dose of a xanthine oxidase inhibitor alone. Licensed xanthine oxidase inhibitors include allopurinol and febuxostat.
Dosage in the marketing authorisation	The recommended dose of lesinurad is 200 mg, administered orally daily in the morning. This is also the maximum dose (see section 4.4 of the summary of product characteristics). Lesinurad tablets must be given at the same time as the morning dose of a xanthine oxidase inhibitor, that is, allopurinol or febuxostat. The recommended minimum dose of allopurinol is 300 mg, or 200 mg for patients with moderate renal impairment (creatinine clearance 30–59 ml/min). If treatment with the xanthine oxidase inhibitor is interrupted, lesinurad dosing must also be interrupted.
Price	The company stated that the list price is £27.90 per 30-pack of 200-mg tablets. Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee (section 4) considered evidence submitted first by AstraZeneca and then by Grünenthal, and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

The aim of treatment

Treatment aims to reduce recurrent episodes of gout by lowering serum uric acid levels

3.1 The committee heard from the clinical experts that the main aim of treatment is to control the frequency of gout flares and to reduce tophi and, in practice, this is commonly achieved at lower serum uric acid levels. It heard from a clinical expert that there is debate about the appropriate target: some guidelines (for example, the British Society of Rheumatology) recommend 300 micromol/litre (5 mg/100 ml); others recommend 360 micromol/litre (6 mg/100 ml). The clinical expert advised that symptoms improve faster in some patients when the serum uric acid level is below 300 micromol/litre even though 360 micromol/litre is below the saturation threshold of uric acid. The committee acknowledged that, in clinical practice, the aim of treatment is to reduce serum uric acid levels to below 300 or 360 micromol/litre.

Current clinical management of gout

Drug therapy for gout in the NHS includes allopurinol and febuxostat

3.2 The committee understood that, before starting any uric acid-lowering treatment, clinicians usually offer people with gout advice on improving their diet, drinking less alcohol, exercising more and stopping smoking. It heard from a clinical expert that, if drug treatment is needed, the options include allopurinol or, if that is not tolerated, febuxostat. The committee heard that clinicians should offer allopurinol and titrate the dose up (to a maximum of 900 mg per day) until serum uric acid is below the target level. It heard from the clinical expert that the median dose of allopurinol associated with reducing serum uric acid to below a target of 360 micromol/litre is 400 mg. The committee noted comments from the Primary Care Rheumatology (PCR) Society that the maximum tolerated dose for most patients in primary care is between 400 mg and 600 mg of allopurinol daily. It also heard from the patient and clinical

experts that many patients in the UK do not take adequate doses of allopurinol. This is not because they cannot tolerate such doses, but because clinicians and patients focus on treating comorbidities (such as blood pressure and lipids) rather than lowering serum uric acid levels and because clinicians lack awareness of the importance of increasing the dose of allopurinol. The committee heard that, in line with NICE's technology appraisal guidance on febuxostat for the management of hyperuricaemia in people with gout, people are prescribed febuxostat only if:

- they cannot have full dose-escalation of allopurinol because of adverse reactions or
- allopurinol is contraindicated or not tolerated.

The committee understood that, although sulfinpyrazone and benzbromarone are treatment options, they are not widely available in the NHS. The committee understood that, to prevent an increase in gout flares that can occur when treatment with febuxostat or allopurinol starts, people are offered up to 6 months of colchicine or a non-steroidal anti-inflammatory drug (NSAID). The committee concluded that allopurinol is widely used and well tolerated, and best practice is to increase the dose to achieve a target serum uric acid level, but that such dose adjustments do not routinely happen in UK clinical practice.

Comparators

The relevant comparator is the maximum tolerated dose of allopurinol needed to bring serum uric acid below target levels

3.3 The committee agreed that lesinurad should be considered as a treatment option only in people in whom the maximum tolerated dose of allopurinol or febuxostat had not brought serum uric acid below the target level. The committee concluded that the relevant comparators for lesinurad were:

- the maximum tolerated dose of allopurinol needed to bring serum uric acid below the target level
- the maximum tolerated dose of febuxostat (only in people in whom allopurinol is contraindicated or not tolerated).

Although the company presented evidence of clinical effectiveness for lesinurad

compared with febuxostat (from the CRYSTAL trial), it did not include febuxostat as a comparator in its cost-effectiveness analysis. Because lesinurad has a marketing authorisation for use with allopurinol and febuxostat is offered only to people in whom allopurinol is contraindicated or not tolerated, the committee did not discuss the comparison with febuxostat.

Evidence from trials of lesinurad

Lesinurad's effectiveness may have been overestimated in CLEAR 1 and 2 because allopurinol dosing was not maximised

3.4 The company presented 2 multicentre randomised double-blind placebo-controlled trials (CLEAR 1 and 2). These compared lesinurad (200 mg per day) plus allopurinol (n=405) with placebo plus allopurinol (n=407) in people with gout who had a serum uric acid level of 360 micromol/litre (6 mg/100 ml) or above and who had at least 2 flares in the past 12 months. The committee heard that, although patients were encouraged to be on a maximised dose of allopurinol before randomisation, the company did not collect data on whether this had been achieved. Also, the mean dose of allopurinol at baseline was about 310 mg per day and was not changed during the trial. The committee noted that this was below the median dose of allopurinol associated with reducing serum uric acid levels to below a target of 360 micromol/litre (see section 3.2). The committee heard from the company that a subgroup analysis comparing patients on a higher allopurinol dose (more than 300 mg daily) with patients on a lower dose (300 mg daily or lower) did not show a difference in treatment effect of lesinurad. However, the committee considered that the subgroup of patients taking a higher allopurinol dose was too small (n=86) to conclude similar effectiveness by allopurinol dose. In response to the second appraisal consultation document, the company used a study by Hande et al. (1984) to estimate how many patients in CLEAR had the recommended allopurinol dose, taking into account renal impairment. The company estimated that more than 92% of patients in the CLEAR trials were taking at least the recommended allopurinol dose because about 60% of the trial population had renal impairment, defined as a creatinine clearance of below 90 ml/min. However, the committee was aware that, in clinical practice, renal impairment is defined as a glomerular filtration rate (similar to creatinine clearance) of below 60 ml/min/1.73 m^2, and that the Medicines and Healthcare products Regulatory Agency in its public assessment report for allopurinol recommends modifying the dose of allopurinol when the creatinine clearance falls below 20 ml/min or lower. The

committee also noted the results of the LASSO study that the company used in its model. This study investigated whether titrating the allopurinol dose up was effective in reducing serum uric acid levels. The study found that allopurinol was well tolerated and that people taking higher doses of allopurinol were more likely to achieve serum uric acid levels below target than people on lower doses. The ERG noted that, in the study by Hande et al., the most relevant research included only 17 people, and that the findings from the study had not been reproduced in a subsequent study. It also noted that a recent guideline from the British Society of Rheumatology suggested that allopurinol dose should not be based on renal function. This is because historically, it has led to people with poor renal function having low doses of allopurinol, which have not reduced their serum uric acid to below target levels, and also that dosing according to creatinine clearance does not reduce hypersensitivity to allopurinol. The committee understood from the guideline that gradually increasing the dose of allopurinol reduces serum uric acid to below target levels in most people and is generally well tolerated. The committee agreed that people in the CLEAR trials were unlikely to have had a maximum tolerated dose of allopurinol, either before or during the trials. It also noted that, had they done so, their serum uric acid would more likely have been reduced below target levels. The committee concluded that the relative effectiveness reported in the trials of lesinurad plus allopurinol compared with allopurinol alone was likely overestimated because the people in the comparator groups did not take a maximum tolerated dose of allopurinol.

Lesinurad lowered serum uric acid levels but did not lower gout flare frequency or improve tophi healing in CLEAR 1 and 2

3.5 Bearing in mind the concerns described in section 3.3, the committee noted that, in the trials, lesinurad plus allopurinol lowered serum uric acid below the target level of 360 micromol/litre for more people than placebo plus allopurinol (54.2% versus 27.9% in CLEAR 1 and 55.4% versus 23.3% in CLEAR 2, $p<0.0001$ in both trials). The committee was aware that the aim of treatment is to reduce the frequency of flares and resolve tophi (see section 3.1), and that gout flares needing treatment and tophus healing were among the secondary end points in both trials. It noted that the trials did not show that lesinurad reduced gout flare frequency (CLEAR 1, $p=0.98$; CLEAR 2, $p=0.57$) or sped up tophi healing (CLEAR 1, $p=0.86$; CLEAR 2, $p=0.84$). At the second appraisal committee meeting, the committee heard from the company that lesinurad could have been

proven effective if the trials had been longer than 12 months. In addition, the company noted that 9 of 10 clinical experts participating in its Delphi panel survey agreed that it would likely take longer than 12 months to see an improvement in clinical outcomes. The committee also heard from the PCR Society that it was 'unrealistic' to expect trials in gout, a chronic disease, to be powered for clinical outcomes, for example, flares. The committee agreed with the PCR Society that longer and larger trials would be needed, but disagreed that these trials were not possible to do, noting examples in other chronic diseases (for example, hyperlipidaemia and hypertension). The committee concluded that lesinurad lowered serum uric acid levels, but that there is currently no evidence that lesinurad improves outcomes that affect the quality of life of people with gout.

The company's economic model

The company assumed that lowering serum uric acid levels improves quality of life and reduces the risk of death

3.6 The company's semi-Markov model assessed the cost effectiveness of 200 mg per day of lesinurad plus allopurinol compared with allopurinol alone. In the model that the company presented in response to the second appraisal consultation document, lesinurad lowered serum uric acid levels, which in turn:

- reduced the number of flares, and so improved quality of life
- increased tophi healing, and so improved quality of life
- improved quality of life independently
- reduced the risk of death.

The modelled population included people with chronic gout with 2 or more flares within the past year despite treatment with allopurinol. The company defined 10 health states by level of serum uric acid (5 categories), and presence or absence of tophi. Each health state in the model was associated with a rate of flares that depended on serum uric acid level, treatment received, time on treatment, and the presence or absence of tophi. Utility values in the model were based on serum uric acid level, the flare rate, the presence or absence of tophi, and other patient characteristics. Tophi incidence and resolution were simulated as transitions between the health

states of tophaceous and non-tophaceous gout, and differed by serum uric acid level. The committee heard that the company had set the rate of tophi resolution to zero for health states with serum uric acid levels above 360 micromol/litre. A patient in any health state could have a gout flare or die, and all model inputs were specific for men and women. The committee noted that the comparator in the model was an unchanging dose of allopurinol, and agreed that the more appropriate comparator was a higher dose of allopurinol (see section 3.2 and section 3.3).

Modelled population: sex

A lack of trial data for women increased uncertainty in the model results

3.7 The modelled population was 21.4% female, based on 'UK demographic and epidemiological data' (Kuo et al. 2014); the ERG was concerned that there were too few women in the trials (4.9%) to predict outcomes for women accurately. The committee heard from the ERG that a population with gout representative of the UK would include more women than did the trials. The committee noted that women in the model contributed substantially to the modelled average survival gains because the company assumed that gout-related mortality is higher in women than in men. The committee accepted that the proportion of women in the model reflected the UK population, but concluded that the paucity of trial data for lesinurad use in women with gout increased the uncertainty in the model results.

Incidence of tophi

The evidence used to estimate incidence of tophi is likely outdated

3.8 The committee noted that the company estimated the incidence of tophi in the modelled population using data from a study by Yu and Gutman (1967). The ERG believed that the age of this study limited its relevance to current practice. However, the committee heard from the ERG that it had not identified a better source of evidence. It also heard from the clinical experts that it was difficult to determine the degree to which the changes in clinical practice and lifestyle have changed the incidence of tophi over the last 50 years. In its updated exploratory analyses, the ERG arbitrarily chose an incidence rate that was 50% of that reported in Yu and Gutman. The ERG noted that Yu and Gutman included people who had not had previous treatment for gout and had never had tophi, whereas the patients in the company's model were starting second-line

treatment and about 19% of patients in the model had tophi. The ERG suggested that managing gout has advanced over the last 50 years; the PCR Society agreed with the ERG that the estimates of tophi were not 'valid'. The committee noted comments from the PCR Society that the incidence of tophi may have increased since the Yu and Gutman study, but noted that the committee had not been presented with evidence for this. The committee concluded that, because the incidence of tophi from Yu and Gutman was collected such a long time ago in an untreated population, and in the absence of a better source of data, there remained uncertainty over the incidence rates for tophi. The committee was also aware that incidence rates for tophi had a negligible effect on the estimates of cost effectiveness.

The effect of lesinurad on serum uric acid levels beyond the trial

The model should account for the possibility of increasing serum uric acid levels over time while on treatment

3.9 The company's model assumed that the serum uric acid level obtained by patients in the first year of treatment was maintained for as long as patients remained on treatment. The ERG noted that there was little evidence to support this because the longest follow-up study of lesinurad lasted only 2 years. It heard from 1 clinical expert that some people have serum uric acid levels that remain stable in the long term, whereas others have levels that increase over time, for example, when kidney function deteriorates. The committee was aware that the ERG did a scenario analysis in which serum uric acid levels increased over time, reflecting a waning effect of lesinurad. In the absence of long-term evidence, the committee agreed to assume serum uric acid levels could increase over time while on treatment.

Stopping treatment because of treatment failure

Treatment should stop in the model if there is an inadequate response to treatment

3.10 The committee heard from a clinical expert that, if serum uric acid remained above the target level, clinicians would offer patients alternative treatments if possible (such as a different uricosuric drug) rather than continue with the current treatment. The committee also heard that clinicians in the NHS would consider stopping treatments that do not work. In response to the second appraisal consultation document, the company introduced a stopping rule into

the model; patients in whom 6 months of treatment with lesinurad plus allopurinol did not reduce their serum uric acid level below 360 micromol/litre stopped taking lesinurad but continued taking allopurinol. These patients had the same benefits in the model had they been randomised to the allopurinol group, but their serum uric acid levels could not improve after stopping lesinurad. The ERG noted that, in the CLEAR trials, most patients who stopped taking lesinurad stopped taking allopurinol as well, so the model inputs were not based on trial data. The committee noted that the stopping rule had a modest effect on the incremental cost-effectiveness ratio (ICER) results. The committee concluded that treatment should stop in the model to reflect clinical practice if there is an inadequate response to treatment, and that the company's approach was acceptable.

Serum uric acid levels, flares, incidence of tophi and tophi healing

The association between lowering serum uric acid levels and outcomes is uncertain

3.11 The committee heard from the clinical experts that there was no validated disease model for patients with gout associating changes in serum uric acid levels and other risk factors with outcomes. It heard that, although serum uric acid level is widely used as a target clinical marker when treating gout, its use as a surrogate outcome measure should be treated with caution. The committee noted that the CLEAR trials did not show that lesinurad reduced flares, improved tophi healing or delayed death but that the trials may have been too small or too short to show these effects (see section 3.5). Therefore, in its responses to the first and second appraisal consultation documents, the company provided additional information to support the relationship between serum uric acid levels and:

- gout flares (see section 3.12)
- tophi healing (see section 3.13)
- mortality (see section 3.15 and section 3.16).

Gout flares

The evidence is insufficient to estimate the strength of the relationship between lowering serum uric acid levels and gout flares

3.12 Because the trial evidence did not show that lesinurad reduced gout flares (see section 3.5), the company provided an exploratory analysis of the CLEAR trials and the extension study 306 that showed that, irrespective of treatment used, people with lower median serum uric acid levels had fewer flares that needed treatment. The committee noted that this cross-sectional analysis did not account for informative censoring (that is, that the patients with more severe disease might have been less likely to remain in the study). The committee agreed that it was not possible to conclude from this analysis that the number of flares fell when serum uric acid levels were reduced. The committee then considered evidence from the company's systematic review. It noted that only 8 of 12 studies in the review reported a statistically significantly lower risk of gout flares with lower serum uric acid levels. However, the committee agreed with the ERG's concern that the risk of bias in these studies had not been examined. The committee noted that neither the company nor the ERG provided a statistical synthesis of trial evidence for the link between serum uric acid levels and gout flares (such as a meta-analysis). On balance, the committee appreciated that it was plausible that lowering serum uric acid levels could reduce gout flares, and that this was generally accepted (notably by the NICE-accredited guidelines on gout from the British Society of Rheumatology). It also noted that changing the incidence of gout flares did not have a big impact on the ICERs. However, the committee agreed that it had not been presented with sufficient evidence to estimate the strength of this relationship and would have preferred to see estimates from a well-conducted meta-analysis of relevant randomised trials.

Tophi healing

The company's approach to modelling the relationship between lowering serum uric acid and tophi healing is acceptable

3.13 In the company's model, 'tophi healing' meant that all tophi completely resolved and patients moved from a health state with tophi to a health state without tophi in which patients had a higher quality of life. The committee heard from a clinical expert, and noted from the guidelines from the British Society of

Rheumatology, that it was plausible that achieving lower serum uric acid levels was associated with a faster reduction of tophi. The committee understood that the company modelled tophi resolution over 2 time periods: the year following initial treatment; and all subsequent years. In response to the second appraisal consultation document, the company analysed data from the CLEAR extension study (study 306) and an extension study of the CRYSTAL trial, which compared lesinurad with febuxostat (study 307):

- In the first year, the company assumed a linear relationship between serum uric acid levels and tophi resolution to estimate rates of tophi resolution.
- For subsequent years, the company used actual tophi resolution rates, based on serum uric acid levels from study 306 and study 307.

The committee noted that the ERG was concerned with the approach taken by the company. It heard that studies 306 and 307 were substantially different, that is, patients in the CRYSTAL trial were younger and had more severe gout than patients in the CLEAR trials. Also, some patients in CRYSTAL took a 400-mg dose of lesinurad, twice the maximum dose approved in the marketing authorisation. The committee understood that the company's approach could have overestimated the effectiveness of lesinurad on tophi healing, but noted that this had a limited effect on cost effectiveness. Although the committee preferred using data from the CLEAR trials alone to model tophi resolution in the first year, and to extrapolate to model subsequent years, it concluded that the company's new approach was acceptable.

Mortality

People with gout have a shorter life expectancy

3.14 In its response to the second appraisal consultation document, the company presented evidence for the association between life expectancy and: gout; high serum uric acid levels; and taking drugs to lower serum uric acid levels. None of the evidence provided by the company came from randomised trials. The committee was aware that the company incorporated 2 assumptions about mortality into its model: first, the life expectancy of the average patient with chronic gout and recurring flares (see section 3.15); and second, to what extent treating to lower serum uric acid prolongs life in people with chronic gout and recurring flares (see section 3.16). With respect to the first of these issues, in response to the second appraisal consultation document, both the company and

the PCR Society offered a biological rationale for how high serum uric acid levels might decrease life expectancy. They argued that high serum uric acid levels increase the immune response and inflammation, and that chronic inflammation is associated with further comorbidities, such as cardiovascular risk, in other conditions like rheumatoid arthritis. The committee considered comments from the PCR Society highlighting a recent epidemiological study by Vincent et al. (2017), which showed that tophi were associated with mortality, but serum uric acid levels were not. The committee accepted that people with gout have an increased risk of mortality compared with people without gout, and that the increased risk reflects both gout and the many comorbidities associated with gout.

The increased mortality with gout used in the model should reflect a UK population with gout and recurring flares

3.15 The company presented the results of 7 observational studies it had identified in a systematic review, which suggested that people with a higher serum uric acid level had a shorter life expectancy than people with a lower serum uric acid level. The company used the results from 1 of the 7 observational studies by Stack et al. (2013) to estimate the life expectancy for people in the model compared with the general population (and also to estimate the magnitude of the benefit of lowering serum uric acid levels; see section 3.16). Based on this study, the company modelled that, above a serum uric acid level of 5 mg/100 ml (300 micromol/litre), mortality risk increased by 16% for every 1 mg/100 ml increase in serum uric acid level. The committee was concerned that this study was a national survey of the US general population, which did not reflect the population in this appraisal because only 2.7% of people had gout and it included people with normal serum uric acid levels. The ERG used a study by Kuo et al. (2016) in its base case to model life expectancy associated with gout, based on sex and the presence or absence of tophi. This study describes patients diagnosed with gout in the UK using data from medical records. The committee concluded that the increased mortality with gout used in the model should reflect a UK population with gout and recurring flares.

There is insufficient evidence to support a relationship between lowering serum uric acid levels and prolonging life

3.16 The committee considered the relationship between lowering serum uric acid levels and prolonging life:

- The company presented a meta-analysis of 6 observational studies, which suggested that, for people with hyperuricaemia or gout, taking uric acid-lowering therapy was associated with a lower mortality risk (pooled, statistically significant hazard ratio: 0.79).
    - The committee noted that the meta-analysis was based entirely on pharmacoepidemiological studies, and that it had not been presented with evidence from randomised controlled studies to validate the relationship between lowering serum uric acid levels and life expectancy, even with drugs other than lesinurad. The committee had concerns about using observational studies to prove that uric acid-lowering therapy prolongs life in people with gout.
    - The committee noted that, when the ERG limited the meta-analysis to studies from the UK (n=13,886), the result did not suggest that uric acid-lowering treatment extended life (non-statistically significant hazard ratio: 0.93). The committee agreed that UK-based studies were more relevant to the population that would be eligible for lesinurad in NHS clinical practice. It also considered that other unknown confounders could have influenced the relationship between uric acid-lowering treatment and life extension reported in the meta-analysis.
- The company used the study by Stack et al. (2013; see section 3.15), to model the decrease in mortality risk when lowering serum uric acid levels with treatment. The company assumed that treatment with lesinurad would reduce by 34% the risk of mortality that was attributable to high serum uric acid levels reported in the study by Stack et al. The company translated this in the model to an increase in mean life expectancy with lesinurad of 0.12 years (1.4 months). The committee agreed that the population in the study by Stack et al. did not reflect the population in this appraisal because only 2.7% of people had gout and it included people with normal serum uric acid levels. It was aware that there is a risk of confounding with results from observational studies because of both known and unknown confounders, and that this could have influenced the relationship between serum uric acid levels and life expectancy reported in the meta-analysis and in Stack et al. The committee noted that the analysis by Stack et al. did not control for, among other potential confounders, poor renal function, which increases the risk of dying and was itself highly associated with serum uric acid levels in the same study.
- The committee recognised that accepting that uric acid-lowering therapy extends life, based on the general population in the study by Stack et al., would imply that people

with hyperuricaemia, but not gout, would also benefit from uric acid-lowering therapy. However, the committee was aware that the guidelines from the British Society of Rheumatology do not advocate treating hyperuricaemia in the absence of gout.

- The committee heard from the company during the committee meeting that it had not included evidence that lesinurad extends life in its application for a marketing authorisation from the European Medicines Agency.
- The committee was aware that NICE technology appraisals for rheumatoid arthritis, another chronic inflammatory condition, had assumed increased mortality risk from having rheumatoid arthritis, but not that treating rheumatoid arthritis with disease-modifying treatments prolongs life.

Therefore, the committee did not accept the company's base-case model, which assumed that treatment with lesinurad prolonged life. The committee agreed that it had not been presented with robust clinical evidence about whether, or to what extent, lowering high serum uric acid levels with treatment extends life expectancy for people with chronic gout and frequent flares. The committee concluded that it was appropriate to use the evidence from observational studies to assume that people with gout have a shorter life expectancy. However, it also concluded that it was not appropriate to assume that reducing serum uric acid levels with lesinurad extends life because there is no robust evidence from randomised trials to validate this.

Utility values

SF-6D utility values from the CLEAR trials are preferable

3.17 In the company's original model, utility values came from the physical component scale of SF-36 from the CLEAR trials, based on flares and tophi, mapped onto EQ-5D. The committee noted that the EQ-5D utility values were implausibly low and showed only a small difference between people with at least 6 flares per month and tophi, and people with no flares and no tophi. The committee had expected a greater difference, given the advice from the patient expert that flares have a substantial impact on quality of life. In response to the first appraisal consultation document, the company used SF-6D scores calculated from SF-36 data from the CLEAR trials to estimate utility values based on numbers of flares and the presence or absence of tophi. The committee agreed this approach resulted in more plausible utility values than the company's original approach. However, after the second appraisal

consultation document, the company provided a linear regression analysis of SF-6D data from the CLEAR trials, this time based on serum uric acid levels, which it argued showed that high serum uric acid levels reduced quality of life independently of the effects of flares and tophi. In its base-case model, the company used these utility values based on serum uric acid level, with adjustments for flares and tophi, and also for age, sex, geographical region, unemployment, BMI and comorbidities (diabetes and hypertension). The committee considered that the association between serum uric acid levels and quality of life may still have been confounded by other variables for which the final analyses did not adjust, for example, cardiovascular disease. It considered that lowering serum uric acid levels would not affect the reduced quality of life associated with these conditions, and that any reduced quality of life was associated with gout flares. The committee was aware that NICE's technology appraisal guidance on febuxostat for managing hyperuricaemia in people with gout concluded that 'there remained some uncertainty about the relationship between absolute serum uric acid concentration and gout symptoms in general, and that this was an additional source of uncertainty in the estimation of the incremental QALYs gained'. The committee was also aware that, in the CLEAR trials, lesinurad did not improve quality of life over 12 months of treatment despite it having reduced serum uric acid levels. It noted that the ERG considered it was implausible that changes in serum uric acid levels affect quality of life and the association was likely to be confounded. The committee agreed that it was not acceptable to base utility values on serum uric acid levels. The committee concluded that utility values based on SF-6D scores calculated from SF-36 data from the CLEAR trials based on numbers of flares and the presence or absence of tophi were more plausible.

Cost-effectiveness results

Lesinurad is not a cost-effective use of NHS resources

3.18 The company's deterministic base case showed that the ICER for lesinurad plus allopurinol compared with allopurinol alone was £12,084 per quality-adjusted life year (QALY) gained (incremental costs £1,598; incremental QALYs 0.13). The committee agreed that this ICER was not plausible because:

- the ICER depended on the assumption that treating gout by lowering serum uric acid levels prolongs life (see section 3.16)

- the dose of allopurinol was not maximised (see section 3.4)
- the model did not allow for serum uric acid levels to increase for the people who remain on treatment long term (over 2 years; see section 3.9)
- the company's base case included utility values based on serum uric acid level (see section 3.17).

In its preferred base case, the ERG made 4 adjustments to the company's base case, which resulted in an ICER of £46,075 per QALY gained for lesinurad plus allopurinol compared with allopurinol alone. These adjustments were:

- 1. using utility values from a linear regression model of SF-6D scores from SF-36 results in CLEAR, based on flares and tophi (see section 3.17; as used by the ERG in its critique of the company's new evidence submitted in response to the first appraisal consultation document)
- 2. modelling tophi healing according to the CLEAR trial, including extrapolating beyond 1 year (see section 3.13)
- 3. assuming the incidence rate of tophi has decreased by 50% since the estimate in 1967 (see section 3.8)
- 4. applying a mortality rate for people with gout and tophi from Kuo et al. (2016) adjusted for sex, instead of serum uric acid level-based mortality rates from Stack et al. (2013; see section 3.15).

The ERG also presented an additional analysis, with adjustments 2 and 3, but instead of 1 and 4:

- using utility values based on SF-6D values using trial-based utilities and not calculated from a linear regression model (see section 3.17)
- assuming that treatment with lesinurad does not prolong life (see section 3.16).

When combined, these adjustments resulted in an ICER of £62,298 per QALY gained for lesinurad plus allopurinol compared with allopurinol alone. The committee was aware that, although the adjustments individually had a modest effect on the ICER, when combined, the individual adjustments interacted to have a substantial effect on the ICER. The committee noted that taking into account the below concerns would increase the ICER even further:

- if the comparator in the model reflected an optimised (that is, maximally tolerated or adequate) dose of allopurinol because the treatment effect would likely have been smaller (see section 3.3 and section 3.4)
- if the modelled serum uric acid levels increased over time to account for a loss of effect of lesinurad (see section 3.9).

The committee concluded that its most plausible ICER for lesinurad plus allopurinol compared with allopurinol alone was likely to be more than £62,298 per QALY gained, which is above the range NICE normally considers to be a cost-effective use of NHS resources, and therefore it could not recommend lesinurad.

Innovation

There were no additional benefits of lesinurad that were not captured in the measurement of QALYs

3.19 The committee heard from a patient expert that gout is undertreated in practice, that allopurinol does not work for everyone and that patients would benefit from new treatments. It noted that lesinurad is the only drug in its class that has been licensed for use with a xanthine oxidase inhibitor, and that it has a different mechanism of action to other reabsorption inhibitors. The committee concluded that it had not been presented with any evidence of additional benefits of lesinurad that were not captured in the reference-case calculation of QALYs.

4 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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Accreditation