Professional organisation statement template

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:
[redacted]

Name of your organisation
British Society for Rheumatology

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **YES**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify) **Expert in Evidence-based Guideline Development for Diagnosis and Management of Gout**

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Gout is highly prevalent and is the commonest inflammatory arthritis in men. It occurs world-wide and is increasing in incidence and prevalence in many countries, largely due to increased longevity and increased prevalence of metabolic syndrome. Gout is mainly treated in primary care. The objectives of treatment are: [1] to manage the pain associated with acute attacks of gout; [2] give advice on how to modify lifestyle/diet and to reduce other modifiable risk factors to reduce serum uric acid (SUA) levels; and [3] to reduce and maintain tissue uric acid levels below the saturation point at which urate crystals can form, thus preventing further urate crystal formation and dissolving existing crystals (ie "cure"). There are recent European and British guidelines on management of gout – these overlap considerably and agree on essential elements of management. Unfortunately, recent audits of quality of care in the UK show that only around one third of patients with gout receive urate lowering therapy (ULT); of those that receive treatment almost all are on a fixed dose (300mg daily) of allopurinol, which is insufficient for many patients.

Allopurinol is the main (often only) ULT used by UK GPs and physicians. It is a non-specific purine xanthine oxidase inhibitor, acting via competitive inhibition of oxidised xanthine oxidase. It is available in the dose range of 100-900 mg daily and is very efficient in lowering SUA. It can be used in patients who are under-excretors of uric acid (the usual situation) or over-producers of uric acid (much less common). It is advised to start allopurinol at 100mg daily and to increase in 100 mg increments, titrating against the SUA, until the target SUA is reached (<6.0 mg/dl or <360 umol/l). The lower the SUA is below this point the faster the reduction in tophus size and the faster the elimination of urate crystals from joints (ie the sooner the patient is "cured" of gout).

Allopurinol can cause mild upsets (e.g. rash, GI disturbance), estimated in different surveys to occur in c.1-5% patients. The "allopurinol hypersensitivity syndrome" (fever, vasculitic rash, renal and hepatic involvement) is rare (< 1:10000) but potentially serious and even fatal. Allopurinol should be used with additional caution in patients with renal impairment, mainly because of prolonged excretion of its metabolite oxipurinol (which inhibits reduced xanthine oxidase) and a subsequent increased risk of toxicity including allopurinol hypersensitivity syndrome. There are possible interactions between allourinol and other drugs (eg azathioprine, 6 mercaptopurine, warfarin). Allopurinol is an old, inexpensive and well-established drug and it is an effective treatment in the majority of patients in whom it is used. As with all ULT, acute attacks may be precipitated during initiation of treatment, especially if higher doses (eg 300 mg) are used in place of gradual titration of dose. Therefore some advise consideration of prophylaxis against acute attacks, using colchicines or an NSAID, during initiation of ULT.

Uricosuric drugs (eg sulpinpyrazone, probenecid) are less efficient ULT than allopurinol, are not widely available, and are contra-indicated in patients with renal

impairment. Benzbromarone is a very efficient uricosuric that can be used in mild to moderate renal imiarment, but it has limited availability and is reported to cause hepatotoxicity (mainly japans patients) that can be fatal.

Losartan and fenofibtare can cause modest reductions in SUA and can be appropriate adjunctive treatment in those gout patients that require treatment of hypertension or hyperlipidaemia respectively (these are common co-morbidities in patients with primary gout).

Vitamin C supplementation (0.5mg daily) can also cause modest reductions in SUA, in the order of c.20%.

Uricase, administered intravenously or subcutaneously, can cause dramatic reductions in SUA but has disadvantages of immunogenecity, expense and requirement of injection delivery. Pegylated versions of uricase are currently under investigation as possible ULT for patients who cannot tolerate allopurinol.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Patients with renal impairment are at greater risk of allopurinol toxicity and cannot be treated with uricosurics (apart from benzbromarone on a named patient basis). Febuxostat is effective in patients with renal impairment and may, overall, have reduced serious toxicity (it is a selective, non-purine inhibitor of xanthine oxidase and metabolised largely by the liver). However, febuxostat has been used in relatively limited numbers of patients and possible hepatotoxicity (elevated liver transaminases) has been observed in clinical trials.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

The drug could be used both in community and hospital settings. Unless it proves to be much safer and better tolerated than allopurinol, its main indication would seem to be for patients who are unsuitable or intolerant of allopurinol therapy. There is a need for appropriate patient education/information access with respect to gout (especially since it is the only “curable” form of otherwise chronic and disabling arthritis) but apart from education there is no special additional requirement for patients with respect to febuxostat.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Febuxostat is not yet available.

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The European League Against Rheumatism (EULAR) has published evidence-based Recommendations for both Diagnosis of gout (1) and Management of gout (2). These guidelines were produced by an international group of experts from 13 European countries using the recommended EULAR process. Propositions were devised using a Delphi technique and a systematic search of the research evidence was then undertaken, with pooling of results and calculation of effects sizes, ICER, likelihood ratio etc, wherever possible. Strength of recommendation was determined by consideration of the research evidence, expert opinion and perceived patient opinion.

1. Zhang W, Doherty M, Pascual E, Thomas T, Barskova V, Conaghan P et al. EULAR recommendations for gout. Part 1. Diagnosis. Ann Rheum Dis 2006;65:1301-11.

2. Zhang W, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P et al. EULAR recommendations for gout. Part 2. Management. Ann Rheum Dis 2006;65:1312-24

The British Society for Rheumatology has also produced recent evidence-based guidelines for management of gout (3). These were produced using the AGREE system involving multiple discipline involvement, patient group commentaries, and systematic search of research evidence. Importantly, despite having different country representation and using different recommended guideline methodology, both the European and British guidelines agree substantially on the core elements of management.

3. Jordan K, Cameron S, Snaith M, Zhang W, Doherty M, Seckl J, Hingorani A, Jaques R, Nuki G. BSR and BHPR Guideline for the management of gout. Rheumatology 2007;doi:1093.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Febuxostat is likely to be made available in two doses (80 and 120 mg). At these doses the drug is relatively efficient at lowering urate and is likely to provoke acute attacks of gout. Therefore in clinical trials of febuxostat it has been standard practice to give prophylaxis with colchicine or an NSAID (drugs which themselves may give side-effects and have interactions with concomitant medications) – this is not necessarily required with allopurinol using the incremental titration scheme (100mg increments approximately every few weeks) stated above. Also, in a clinical trial comparing febuxostat at these 2 doses against a fixed 300mg dose of allopurinol (Becker et al. N Engl J Med 2005;353:2450-61), almost half of the patients on the higher 120 mg dose still did not reach the therapeutic target of a SUA <6.0 mg/dl after one year of treatment. Although the proportion reaching this target was greater

than in the group receiving allopurinol 300 mg, in clinical practice there is the option to increase allopurinol in 100 mg increments up to 900 mg daily (ie x3 the dose used in this study) until the target is achieved. It is unclear as to what to do with patients that fail to reach the therapeutic target on fexuxostat 120 mg daily – can the dose be increased further and what dose increments can be made? Notably in the Becker et al study there were more drop-outs and more abnormal liver function tests on the higher dose of febuxostat, which is of some concern.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Because of its efficiency at 80 and 120 mg daily doses it may be recommended to give prophlaxis against acute attacks (colchicine or NSAID) for the first few months of commencing febuxostat. The SUA should be monitored to ensure that the therapeutic target has been achieved (<6.0 mg/dl). If the target is not achieved then further ULT needs to be given – either by increasing the dose of febuxostat from 80 to 120 mg daily or, if already on 120 mg febuxostat daily, by substitution or addition of another agent (eg a uricosuric or allopurinol), depending on the individual patient history, comorbidity and response to previous ULT.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Febuxostat 40mg, 80mg or 120mg daily has been compared to placebo in a one month RCT (Becker et al. Arthritis Rheum 2005;52:916-23) and febuxostat 80mg or 120mg has been compared to a fixed dose of allopurinol 300mg daily in a one year RCT. The results of a trial that would better reflect clinical practice (ie by comparing efficacy and tolerability of febuxostat against a titrated dose of allopurinol, up to maximum dose if required) are still awaited. The two published trials used the appropriate primary outcome measure by which to judge efficacy of ULT – that is, the lowering of SUA below the saturation point for urate crystal formation. They also included reasonable secondary endpoints (tophus size reduction, frequency of acute attacks) and documented adverse events and drop-out rates. Unfortunately, the use of a fixed dose of allopurinol 300mg daily *does* reflect common UK GP practice, even though the recommendations from EULAR and BSR are to use an escalating dose of allopurinol, titrated against the SUA, up to a maximum dose (900mg daily, depending on renal function)) if required (NB this is very rarely required in clinical practice).

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

In the one year clinical trial versus allopurinol (Becker et al. N Engl J Med 2005;353:2450-61) there were more discontinuations in the high dose febuxostat

group than in the lower dose febuxostat or allopurinol groups. There were significantly more withdrawals for abnormal liver transaminases in those taking febuxostat (12 patients on febuxostat versus 1 on allopurinol – ie 2.4% versus 0.4%). Four patients on febuxostat died, compared to none on allopurinol, although in all 4 cases the cause of death was not thought to be directly attributable to the drug. In the higher dose febuxostat group there were more exacerbations of acute flares of gout than in the other two groups. All of these problems could result in reduced quality of life, although this was not directly measured. As stated above, an unresolved question is what to do with patients who do not achieve the therapeutic target on 120mg of febuxostat.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

If febuxostat were made available it would offer another therapeutic option to those patients who are unable to tolerate allopurinol (or other ULT) due to troublesome side-effects, but particularly due to the rare allopurinol “hypersensitivity” syndrome”. If abnormal LFTs are confirmed as a potentially severe side-effect this might require blood monitoring (details of the abnormal LFTs and their timing were not provided in the published paper). The drug is given as daily oral medication so no special facilities are required. The prescribing doctor requires education concerning dosages; side-effect profile; requirement, nature and duration of accompanying prophylaxis in the first months of initiation or dose increase; and the therapeutic target SUA.

Therefore, apart from physician education and possible blood monitoring of LFTs this drug could be introduced readily into the management of patients with gout.