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:

Submitted by [redacted], [redacted] on behalf of the organisations below.

Comments coordinated by [redacted]/[redacted]

Name of your organisation:
National Cancer Research Institute
Royal College of Physicians
Royal College of Radiologists
Association of Cancer Physicians
Joint Collegiate Council for Oncology

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ✓
- 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)

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?

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?

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)?

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?

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.

Response

Approximately one-third of patients with myeloma fail to respond to induction chemotherapy, and eventually all patients who achieve remission will relapse. Patients refractory to initial chemotherapy due to drug-resistance have a poor prognosis, with few responding to other therapies. Patients who respond to chemotherapy initially, but relapse during the course of treatment or within the following few months, are more likely to respond to second-line therapy than drug-resistant patients (Salmon 1997). Patients who fail to achieve remission on re-induction are considered refractory to treatment (Salmon 1997).

Patients with progressive disease after primary therapy may be re-induced with the initial induction therapy if relapse occurs after greater than 12 months (Kyle 2004). A wide range of salvage therapies have been reported including cyclophosphamide-VAD (C-VAD), etoposide/ dexamethasone/ cytarabine/ cisplatin (EDAP), high-dose (non-marrow-ablative) cyclophosphamide, thalidomide, TD, dexamethasone/ thalidomide/ cisplatin/doxorubicin/ cyclophosphamide/ etoposide (DT-PACE), or bortezomib (Velcade®) (NCCN 2006; Kyle 2004). The incidence of renal impairment increases with relapsed disease and currently available chemotherapy needs to used with caution because of the significantly increased risks of toxicity and complications that occur in this situation Lenalidomide has been shown in a sub-group analysis in the MM 009 and 010 studies to be safe in patients with renal impairment (Weber et al 2007). There was no significant difference in ORR, TTP or OS in

patients with a creatinine clearance above 50ml/ min versus those less than 50ml/ min. For those with a CrCl < 30ml/min however, there was reduced TTP and OS but TTP and OS was still higher in the lenalidomide/dexamethasone treated patients than in those receiving dexamethasone alone. In a further study by Reece et al from Canada's Expanded Access Study, 23 (33% of all) patients had elevated Creatinine (female >89umol/L, males 109umol/L). In those treated with lenalidomide and dexamethasone or prednisolone there was no impact on PFS and CR in renal impaired patients. Furthermore, Lenalidomide and corticosteroid were able to be given to patients with elevated creatinine levels with careful platelet monitoring

Approximately 40% of resistant and relapsing patients may achieve second remission with glucocorticoids. Second-line combination chemotherapy regimens (primarily including alkylating regimens) may help a small percentage of patients: 8% of resistant patients, and 22% of refractory patients. A slightly higher percentage of patients receiving doxorubicin-based regimens may respond but the duration of second response may be less than one year (Salmon 1997). Between 40% and 50% of patients respond to VAD in relapsing multiple myeloma (Zaidi 2001). Addition of cyclophosphamide to VAD (CVAD) has been shown to achieve responses in up to 40% of VAD-refractory patients (Munshi 2001).

Recent phase III clinical trials have demonstrated the effectiveness of novel agents such as Thalidomide (Thal), Lenalidomide (Len) and Bortezomib (Bz). There are a variety of clinical settings in which relapse can occur and the outcome of further treatment will be determined by the presence of adverse patient co-morbidities such as peripheral neuropathy or thrombo-embolic disease, cytogenetic evolution of the myeloma clone, and the adverse effects and side-effects profile occurring secondary to the treatment previously received.

Patients achieving a complete remission tend to have longer response duration and overall survival post stem cell transplantation than those failing to achieve a CR.

Lenalidomide is not currently available for patients within the NHS outside of clinical trials although it can be accessed by patients in the Private sector. These patients are generally receiving the drug within the licensed indications. The UK Myeloma Forum is currently updating clinical guidelines for the treatment of relapsed disease and the use of Lenalidomide. In addition, there is a position paper on the use of Lenalidomide (Morgan G et al 2008).

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?

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.

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?

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?

Response:

Lenalidomide is a thalidomide analogue that has been demonstrated in animal models to have teratogenic potential and therefore its use requires the implementation of a pregnancy prevention programme (PPP). Whilst the regulatory authorities have significantly reduced the impact of the previous programme on the efficient running of a busy clinic, this additional burden will significantly increase the work of running a myeloma clinic.

Two phase I clinical studies of heavily pre-treated subjects with relapsed or refractory multiple myeloma have been conducted to identify the maximum-tolerated dose (MTD) and to evaluate the safety of oral Lenalidomide. Myelosuppression was found to be the dose-limiting toxicity (DLT) and the MTD for the first month of therapy was 25 mg/day. No significant somnolence, constipation or neuropathy was observed. However, reversible myelosuppression did develop in patients receiving Lenalidomide 25 mg/day during the second month of treatment. Phase II data indicates that an interrupted schedule of administration ameliorates the marrow suppressive effects of Lenalidomide. In the first phase I study, 17 (71%) of 24 evaluable subjects achieved **>**25% reduction of the myeloma paraprotein and in the second study 20% of the subjects achieved a $\geq$ 50% paraprotein reduction (all responders were receiving 25 mg to 50 mg/day of Lenalidomide).

Two Phase III studies, MM 009/ MM010 studies (Dimopoulos et al 2005; Weber 2006) of Lenalidomide and dexamethasone versus placebo and dexamethasone in relapsed/ refractory disease demonstrated an overall response rates of 58%. Time to progression on an

ITT basis was (11mos v's 4.7 mos) (*P*<0.001 and the median overall survival had not been reached at the time of analysis. There was however, a significantly higher risk of thromboembolic complications in the Len Dex arm particularly if they had received prior Thal The toxicity profile revealed very low incidence of fatigue, constipation, and neuropathy but increased grade 3/4 hematologic events. Due to the increased incidence of VTD, the authors recommended consideration of prophylactic anticoagulation. It is to be noted that 2/3 of the patients enrolled on the trial have experienced and failed thalidomide based therapy.

The combination of Lenalidomide and dexamethasone is given orally and in clinical experience of treating over 70 patients with this agent it is easily administered with minimal toxicity. Neutropenia does occur but it is only rarely associated with fever and infection (MM009 and MM010). This apparent anomaly may be due to the up-regulation of neutrphil activation membrane receptors by Lenalidomide that enhances their anti-infective activity (Desmond A. et al 2006). Neutropenia is reversible with cessation of Lenalidomide. In rare cases, G-CSF can be used to accelerate recovery.

The clinical trials reflect UK experience of the use of this drug. The extended access programme, MM018, in the UK suggests that the clinical trial activity is generalisable. The responses seen with this agent tend to occur within 3-6 weeks although optimal response may not be seen until 6-8 months. In the MM010 and MM009 studies the average number of courses received before resistance or toxicity is eleven. The value of long-term maintenance has not been formally tested in the context of a clinical trial in the relapsed setting, although a trial is ongoing looking at this in the de novo setting.

The most appropriate marker of response is the paraprotein. Data is emerging that suggests that serum free light chain levels (sflc) at presentation may predict for outcome when included in the international staging system and the rate of fall of sflc may be surrogate early predictor for response. Time to Progression (TTP), and overall survival (OS) are appropriate markers (PFS) are appropriate markers of survival.

The experience of using Lenalidomide outside of clinical trials is that tiredness and lethargy are more prominent clinical features than perhaps reported in early clinical trials. It is not the experience of our experts that this is a dose limiting toxicity being generally well tolerated without the need to discontinue treatment.

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)?

Response:
There is a need to educate and train staff in the implementation of the pregnancy prevention programme (PPP). There is a need for a telephone in the clinic to facilitate this programme.

There is also a need for the Pharmacy to establish systems to operate the PPP and training is required for these personnel.