NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Pixantrone monotherapy for the treatment of relapsed or refractory aggressive non-Hodgkins lymphoma [ID414]

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] submitting on behalf of:

Name of your organisation NCRI/RCP/RCR/ACP/JCCO

Comments coordinated by Dr Ruth Pettengell

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)

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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?

Pixantrone provides an evidencebased effective therapy option for patients who relapse post-transplant or those ineligible for transplant who relapse following standard chemotherapy. Currently, the only options for these patients are clinical trials, if available, or symptomatic management often with chemotherapies lacking an evidence base. The Pix301 trial is the only randomised prospective trial in this patient population and as such provides a new standard of care. The comparator agents used in the study remain current.

We need not only new more effective treatments but therapies that positively impact on quality of life. Current survival rates for people with relapsed or refractory aggressive non-Hodgkin lymphoma are extremely low. Patients are usually very symptomatic with current treatments aimed at controlling these. Providing effective therapy is the most efficient way to resolve or alleviate symptoms. Response rates in the trial were 40% compared with 14.3% in the comparator group.

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?

This technology is most appropriate to people whose lymphoma has previously been sensitive to treatment with anthracyclines. Anthracyclines are the most active class of drugs in lymphoma and many patients at relapse remain anthracycline sensitive but are unable to receive further anthracycline therapy because of cumulative cardiac toxicity.

Older individuals, or those with co-morbidities, have very limited treatment options and will benefit from improved disease control with a well tolerated regimen.

Individuals with pre-existing heart conditions, who might be more susceptible to the cardiotoxic effects of anthracyclines, should also benefit.

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 will be used in specialist Haematology / Oncology Centres. Standard cytotoxic procedures apply with no need for additional professional care. Administration, although intravenous is via a peripheral line over 60 minutes on days 1, 8 and 15 of a 28 day cycle. As such these patients can be treated in a day-case

setting as outpatients. The frequency of visits are similar to other chemotherapy alternatives and considerably less than the demands of experimental therapies in the context of clinical trials.

The side effects are familiar to people with previously treated aggressive lymphoma and as shown in the clinical trials are likely to be comparable with alternative regimens.

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?

The technology is not part of routine NHS care so it is not possible to comment. Outside of the clinical trial the drug was not readily available for use within the UK.

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.

There is no standard treatment for this group of patients. Where possible patients are entered into early clinical trials or treated with single agent chemotherapy to manage symptoms. The Pix 301 trial is the only randomised trial in this heavily pretreated patient group. The treatment options currently available are listed in the Final Scope. The level of evidence for their use is poor, the best information coming from small phase 2 trials.

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?

Standard procedures for handling cytotoxics apply with no additional measures required. Administration, although intravenous, is via a peripheral line over 60 minutes on days 1, 8 and 15 of a 28 day cycle. Therefore, these patients can be treated in a day-case setting as outpatients. The frequency of visits is similar to other chemotherapy alternatives and considerably less than the demands of experimental therapies in the context of clinical trials.

The side effects are familiar to clinicians and patients with previously treated aggressive lymphoma and, as shown in the clinical trials, are comparable to alternative regimens. No concomitant treatments are required.

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.

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This technology is most appropriate for people whose lymphoma has previously been sensitive to treatment with anthracyclines, as defined in the trial. Patients who have not had a clinical response within 2 months are unlikely to benefit from further therapy.

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?

The patients entered into the trial, including the 15% of patients who had relapsed post-transplant, reflect current UK practice. The comparator agents used in the trial remain in current use.

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?

Effective treatment of the aggressive lymphoma is the best way to provide symptom control a major problem for this patient group. A response rate of 40% was seen with pixantrone compared with 14.3% in the comparator agents. All individuals who responded did so by 2 months avoiding cost and toxicity from non- beneficial treatment. In addition, the technology offers hope, not just of relief from symptoms, but also of progression free survival (approx. 3 months).

Importantly, complete remissions were observed in 20% of patients versus 7% in the comparator group. Progression free survival in complete responders was double that on the ITT Pixantrone group (10.2 versus 5.3 months, respectively).

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?

Pixantrone has a comparable number of side-effects to the alternative treatments available to this group. The major toxicity from the trials was haematologic. More neutropenia was reported in the trial, but little infection occurred as a consequence of this. These heavily pretreated patients and their clinicians are used to managing these toxicities.

There has been little use of this drug outside of the clinical trials. However, experience with this class of drugs is extensive, and unrecognised side effects are unlikely.

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.

This structure of this drug prevents binding to iron and toxic alcohol metabolites / oxygen free radicals which cause both short and long term cardiac toxicities in other anthracyclines. If further use confirms the favourable cardiac profile of this drug, its future will be in combination with other agents in earlier lines of therapy, since cardiac morbidity in cancer survivors who received anthracyclines is very high. In adults, cumulative doses of 400-450 mg/m^2 of doxorubicin result in a 5% risk of congestive heart failure (Swain SM *et al*., Cancer 2003: 97;2869-2879). In children even lower cumulative doses result in a lifetime risk for cardiotoxicity (Barry E *et al*., Expert Opin Pharmacother 2007: 8;1039-58).

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)?

The technology could be introduced with current resources.