Clinical Expert Submission Template

Thank you for agreeing to give us a personal statement on your 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. Your statement can be as brief as you like, but we suggest a maximum of 8 pages.

If there are special reasons for exceeding this 8-page limit please attach an Executive Summary to your statement.

What is the 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 in 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?

Multiple myeloma is currently incurable but treatment has been shown to improve both quality and duration of life. Treatment controls disease achieving a remission or a 'plateau'. Patients will relapse from these remissions or plateaus after a variable period of time and will require further therapy. The median overall life expectancy is between 3 ½ to 4 years. Initial therapy is allocated depending on biological fitness. Fit patients (usually under 70) are treated with infusional regimes such as VAD and C-VAMP to induce response followed by a stem cell transplant (autologous) following high dose melphalan conditioning. For patients considered unfit for stem cell transplantation melphalan and prednisolone remains the treatment of choice. This therapy is given to plateau/remission and then stopped.
Some patients fail to respond to initial therapy and will be treated with salvage therapies which will usually include thalidomide. Increasingly thalidomide is used as part of initial therapy for myeloma and its place in initial therapy is being tested in the current MRC Myeloma IX trial.
All patients will relapse from first remission/plateau after a variable duration of time. These patients then require second line therapy. Second line therapy will usually involve a thalidomide containing regime (although this may not be effective if the patients received thalidomide as part of their initial therapy) and can be followed by a second autologous stem cell transplant. Thalidomide has emerged as an important therapy for myeloma. It is effective as a single agent but is usually used in combination with dexamethasone as well as other therapies. There is good evidence that it is synergistic with a number of other agents. A second remission or plateau may be achieved in 40-50% of cases and again will last for a variable period of time although the second remission/plateau is usually shorter than the first response. Patients who do not respond to second line therapy or who relapse after second line therapy have a poor prognosis and there is no well established therapy for these patients. Usually these patients will get high dose steroids or oral cyclophosphamide or melphalan to try and achieve a third response but response rates are usually poor – around 20% or less.

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?

There are several markers of poor prognosis in myeloma. These include age, stage, low albumin and a raised Beta – 2 – microglobulin. Patients with myeloma who present in renal failure have a poorer prognosis and their renal failure makes the disease difficult to treat safely. Patients with plasma cell leukaemia have a particularly poor prognosis. Increasingly cytogenetics mark out patients who have a poorer prognosis. Patients with deletion of chromosome 13q or with evidence of a 4;14 translocation frequently do not respond or respond poorly to conventional chemotherapy. Bortezomib is one of the few agents which seems to be effective in patients with myeloma with a poor prognosis. Analysis of the APEX data suggests that response to the technology is the same in patients with a high B2M, patients with renal failure and patients with del 13q or the 4;14 abnormality.
There does not seem to be any subgroup which is more at risk of side-effects from the drug.

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 technology should be delivered in specialist haematology units with an interest in multiple myeloma and should be delivered by specialist chemotherapy trained nurses who have considerable interest and experience in treating patients with multiple myeloma.

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 widely available in Scotland and is widely used. It is usually used according to license as either third or second line therapy for relapsed multiple myeloma. A number of areas in England and Wales have approved the drug for use as third line treatment for multiple myeloma and where approved or where funding is available the drug is being widely used. In other areas PCTs and NHS trusts are awaiting NICE guidance.

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 BCSH has produced a position statement on Bortezomib in multiple myeloma. (See British society of Haematology web-side). This was produced to bring together all the evidence on velcade in multiple myeloma. It was produced by 4 experts in the field who reviewed the literature extensively using searches on the words velcade, multiple myeloma, relapsed multiple myeloma and bortezomib. The major conclusions of this position paper were:-

Bortezomib is licensed for use at first relapse.
Clinical evidence would suggest benefits when combined with dexamethsone as a treatment for second relapse, as well as for the treatment of patients at first relapse who have been exposed to a range of therapies including thalidomide as either induction therapy or as maintenance treatment.
It is given at a dose of 1.3 mg/m2 on days 1, 4, 8 & 11 as an i.v. push.
Strict attention should be given to the spacing of the drugs. It should not be given
at more frequent intervals than 72hours.
Side effects include constipation, diarrhoea and nausea, all of which need to be
managed appropriately.
It can cause peripheral neuropathy and if painful peripheral neuropathy occurs the drug should be stopped immediately.
Prophylaxis for neuropathy may be useful but evidence supporting its use is limited. • Myelosuppression and thrombocytopenia are transient and reversible.
Combinations are possible but appropriate doses are not currently well defined.

The Wolfson unit in Newcastle has also produced a paper on the use of Bortezomib second line in the management of multiple myeloma.

The Scottish Medicines consortium has also produced guidelines regarding Bortezomib in Multiple myeloma

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, if already available, compares with current alternatives used in the UK. Is the technology 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 use?

The safety and efficacy of bortezomib in myeloma patients has been investigated in two phase II studies of patients at relapse after at least 2 previous lines of treatment. The first, 'SUMMIT' enrolled 202 patients and the overall response rate (CR, PR, and MR) was 35%, with 10% CR or near CR (Richardson et al, 2003). Responses were usually seen within the first 2-3 cycles of treatment and the response rate increased to 50% with the addition of dexamethasone (20mg on days 1,2, days 4,5 days 8,9 and days 11,12). In a sub-analysis it was noted that response was independent of the number of previous lines of treatment, and type of previous treatment, confirming in vitro data that bortezomib works via a different mechanism and overcomes resistance to other treatments.

A second study, 'CREST' enrolled 54 patients and evaluated two dose levels (1.3mg/m2 and 1.0mg/m2) using the standard 21-day schedule. Response rates (CR and PR) were similar between the two doses (30% vs 38% respectively) with manageable toxicities (Jagannath et al 2004).

This encouraging phase II data lead to the phase III study 'APEX' being set up. This study in 669 patients compared single agent bortezomib with standard dose dexamethasone in patients at first or subsequent relapse. The study was a cross-over design therefore at relapse all patients were eligible for bortezomib treatment. The study was closed early because of superior responses and disease free survival in the bortezomib treated cases. The response rate (CR+PR) was 38% in the bortezomib arm compared to 18% in the dexamethasone arm. The results are even more impressive if one looks at patients treated at first relapse where the response rate (CR+PR) was 45% in the bortezomib arm compared to 26% in the dexamethasone arm. The overall response rate for all patients entering the study has improved to 43% with further analysis of the data. At the time of analysis 29% of patients receiving bortezomib had progressed compared to 52% of patients receiving dexamethasone, resulting in a median time to progression of 6.2 months versus 3.5 months respectively. This translated into a 22% difference in overall survival at 12 months (Richardson et al 2004). Based on this phase III data it can be concluded that bortezomib is a better treatment than dexamethasone at relapse. In a series of observational studies carried out on patients entered into these three studies it was shown that patients who respond to therapy had improved levels of haemoglobin, decreased transfusion requirements and an improved quality of life based on data collected using a patient-directed questionnaire.

There was a marked improvement in disease free and overall survival for the patients who responded compared to those who did not. The median disease free progression for patients who responded in the SUMMIT was 12 months which is highly significant at second relapse for a disease with a median survival of 3-5 years from presentation.

The technology must be delivered in a specialist cancer/myeloma unit with considerable experience in delivering cancer chemotherapy.
The technology must be given as an intravenous push with injections being given 72 hours apart i.e. on Days 1, 4 7 and 11 of a 21 day cycle.
The technology is no more difficult to apply compared with conventional chemotherapy although will require more frequent hospital visits on behalf of the patient.
There are no more clinical tests required to look after a patient with myeloma requiring therapy with velcade compared with a patient with myeloma requiring any form of chemotherapy.

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.

There is good evidence to suggest that patients who respond to Bortezomib are most likely to respond within the first 4 courses of therapy. All patients who are treated with myeloma should be followed very closely to assess response and this is true with Bortezomib. Some physicians will use additional dexamethasone as therapy for patients who are on Bortezomib. A number of physicians will use dexamethasone with bortezomib from the start and the rest will introduce dexamethasone into the treatment schedule if patients fail to respond after 4 course of treatment. As stated above there is good evidence that the addition of dexamethasone increases the response rate to bortezomib.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology in clinical practice reflects that observed under clinical trial conditions. 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?

The trial data that is available for velcade is now very extensive and there is now considerable clinical experience with the technology. The technology has been used along very similar, if not, identical circumstances to the clinical trials and there is widespread agreement that trial results are borne out in clinical practice.
The trials largely reflected clinical practice in the U.K. although it should be acknowledged that there is no universally agreed standard second or third relapse chemotherapy.
The most important outcomes were measured in the trial and would include response rate, relapse-free and overall-survival. All markers of response were used.

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?

Side effects of Bortezomib include:
Bortezomib therapy results in a different range of side effects compared to that seen with classical chemotherapy. Specialists should be aware of the different spectrum of side effects seen with this technology to ensure its safe use. While the range of side effects of bortezomib is wide, the majority are readily manageable, however because it is delivered in the outpatient setting, it is important to put in place a means of assessing and managing these effects.

Side effects are organ specific as outlined below:

Haemopoietic system
Neutropenia and thrombocytopenia occur after exposure to bortezomib, but are less of a problem than after cytotoxic chemotherapy. Fortunately, as a single agent bortezomib does not damage the haemopoietic stem cell and initial results suggest that prior exposure does not impair the ability to carry out stem cell harvesting. However, despite this it remains important to treat pyrexia as an emergency as would be done with any chemotherapy which can cause neutropenia. Anaemia can occur and erythropoietins can prevent and reverse this. Thrombocytopenia is seen especially in patients with low starting platelet counts, but the mechanism by which this occurs differs from that with cytotoxics. Bortezomib appears to block megakaryocyte budding leading to low circulating levels of platelets but the effect is reversible with platelet counts coming up in the treatment break. It can be anticipated that there will be an approximately 40% reduction from the initial platelet count and that the nadir will be maximum at day 13-14. Cumulative suppression may occur with successive courses especially if the platelet count fails to return to baseline at the beginning of subsequent courses. Platelet transfusion can be helpful and should be used according to standard guidelines.

Immune system
Immune suppression may occur but is not severe. Cases of Herpes Zoster have been reported, and should be treated with acyclovir, however prophylaxis with this agent is not routinely recommended. Prophylaxis with co-trimoxazole to prevent pneumocystis infection is not essential but may be considered as a sensible precaution. There are no data on the use of irradiated blood products and they are not considered necessary unless there are other indications present for the use of irradiated blood or blood products.

Nervous system
Effects on the nervous system are common and require close monitoring. Central effects such as tiredness and fatigue may occur, and can be difficult to manage, but may respond to dose reduction. Peripheral neuropathy is the most severe side effect. This is mainly sensory but motor neuropathy can also occur. Dose reduction or withdrawal according to the nomogram below may be required to control neuropathic problems. Usually symptoms will resolve if the bortezomib is dose reduced or stopped at an early stage, occasionally however, there is persistent damage. Painful progressive peripheral neuropathy is an absolute indication to discontinue treatment. It is not possible to predict who will develop neuropathy but patients with previous peripheral neuropathy are at greater risk although this is not an absolute contraindication to the initiation of treatment. Patients previously exposed to vincristine, thalidomide or who have diabetes are at greater risk and management of myeloma now needs to take into account the long term risks and management of peripheral neuropathy. There are no clear data to guide prophylactic strategies for peripheral neuropathy ; anecdotally folate and vitamin B12 levels may be low in myeloma patients and should be checked and replacement given as necessary. Vitamin supplements can be used including folic acid, vitamin B complex, pyridoxine, together with L-carnitine, α-lipoic acid and L-glutamine, but there is no evidence base

to support this approach. Treatment of established painful peripheral neuropathy follows a standard approach including pharmacological intervention with amitriptyline or gabapentin and if severe, referral to a pain clinic is an appropriate strategy. As a consequence of damage to the autonomic nervous system, postural hypotension may also occur. This can be effectively managed by ensuring adequate hydration and the use of fluid transfusions at the time of the bortezomib infusion (500ml over 1-2hours). Dose reductions may also be effective if this does not work.

Gastrointestinal system
Gastrointestinal side effects are common and variable. Bortezomib may cause nausea and is mildly emetogenic; metoclopramide and ondansetron are effective in preventing this. Diarrhoea and constipation may also occur and this needs to be effectively managed using standard approaches. Bortezomib is metabolised by the liver with only a small proportion being extracted via the kidney. There are no data on the use of bortezomib in patients with impaired liver function, although its use in this setting may be appropriate, it will require careful monitoring.

Renal system
A small proportion of bortezomib is excreted by the kidneys and consequently care should be exercised with its use in patients with impaired renal function. There is limited experience in the use of bortezomib in patients with renal failure and creatinine clearances of less than 30ml/minute. However in cases where it has been used it has been safe and renal function has improved in a proportion of cases. Even at moderate levels of creatinine clearance, care needs to be exerted. At lower levels or in patients on dialysis, experience with the use of bortezomib is limited however it seems to be feasible starting at a dose of 1.0mg/m2 at the standard daily intervals (days 1,4,8,and 11). Obviously patients treated in this way need to be closely monitored. Tumour lysis can occur and should be watched for; consequently allopurinol should be used during initial cycles as well as maintaining hydration.

Cardiovascular system
Cardiac arrhythmias have been described but are rare. Other cardiac complications are similarly rare. Venous thrombotic events are not reported to be increased compared to other therapeutic approaches.

Miscellaneous
A number of miscellaneous side effects have been described including mild skin rashes and fever. Diabetes may be exacerbated by the use of bortezomib.

Suggested dose reduction schedule

Before each dose patients should be evaluated for possible toxicities and the dose of bortezomib reduced or withheld if necessary.
Bortezomib-related neuropathic pain or peripheral sensory neuropathy must be closely monitored as either dose reduction or withdrawal may be required.

The following table contains the recommended dose modifications. If the toxicity does not resolve after dosing has been withheld for 2 weeks, then the patient should be discontinued from treatment.

Recommended Dose Modifications for Bortezomib-Related Neuropathic Pain and/or Peripheral Sensory Neuropathy

Severity of Peripheral Neuropathy
Signs and Symptoms
Modification of Dose and Regimen

Grade 1 (paraesthesia and/or loss of reflexes) without pain or loss of function
No action

Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)
Reduce bortezomib to 1.0 mg/m2

Grade 2 with pain or Grade 3 (interfering with activities of daily living)
Withhold bortezomib therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of bortezomib at 0.7 mg/m2 and change treatment schedule to once per week.

Grade 4
(Permanent sensory loss that interferes with function)
Discontinue bortezomib

Dose modifications if neutropenic

If the neutrophil count falls below 0.5x109/l the drug should be withheld until the neutropenia has resolved and then the dose reduced to 1.0mg/m2 or 0.7mg/m2. If the neutropenia is felt to be due to marrow infiltration rather than poor marrow reserve then continuing with the same bortezomib dose and using G-CSF may be a useful therapeutic option. Dose reduction or temporary withdrawal of bortezomib may also be required for thrombocytopenia, although if this is felt to be due to marrow infiltration by myeloma then support with platelet transfusions while continuing with twice weekly dosing is appropriate.

Other dose modifications

Bortezomib should be withheld at the onset of any grade 3 or grade 4 non-haematologic toxicity for up to 2 weeks until the toxicity returns to at least grade 2. Dose reduction to either 1.0 mg/m2 or 0.7 mg/m2 should then be considered. If grade 3 or 4 toxicity persists then bortezomib treatment should be withdrawn.

All of the side effects noted with Bortezomib were noted during the clinical trials and no emerging side effects have been noted with wider use. Indeed with greater knowledge of the side-effects, the management of these side effects is improving all the time. In particular the neuropathy associated with Bortezomib appears to be largely reversible with close observation and institution of the appropriate measures listed above.

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.

I know of no additional information outside of the published data that might inform this appraisal. To my knowledge there are no published or available audits of Bortezomib use. There are no registries collecting data that might help this appraisal.

Implementation issues

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)?

NICE guidance on this technology is likely to improve the equity of drug availability across England and Wales. Currently there is no standard approach to Bortezomib availability and availability of Bortezomib across England and Wales is uneven.

No extra equipment is required to provide this agent although additional resource may be required to provide for multiple hospital visits. Many departments would like to see improved provision of nerve conduction testing to aid the management of myeloma patients as neuropathy is a consequence of the disease itself, amyloidosis, vinca alkaloids, thalidomide as well as Bortezomib.

No additional training would be required for staff delivering this agent although it will be important to ensure good education of all to ensure safe drug delivery.

The NHS is required by the Department of Health and 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 Welsh Assembly Government to vary this direction.

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

Overall there is overwhelming support amongst haematologists in England and Wales for the technology to be approved. The agent represents a very significant therapeutic breakthrough and is being used widely through the USA and Europe. The agent is also available in Scotland for the treatment of relapsed/refractory myeloma and in some areas of England and Wales. There is widespread alarm amongst patients that there is a degree of 'postcode prescribing' of this agent. The agent, if approved, should only be prescribing in clinics with a special interest in multiple myeloma and by haematologists with an interest in multiple myeloma.