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Our Ref: GJM/DF0160

7th August 2006

Ms Emily Marschke
Technology Appraisals Project Manager
National Institute for Health and Clinical Excellence
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71 High Holborn
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Dear Ms Marschke,

Re: Appraisal Consultant Document: Bortezomib (Velcade) for Multiple Myeloma

Thank you for giving me the opportunity to reply to the ACD for the Velcade submission. I had the opportunity to comment during the panel meeting and the opportunity to explain the clinical setting for Velcade treatment in myeloma was very welcome. Given the rules under which the appraisal was conducted, I found the conclusions appropriate. The definitive conclusions were that:

i) '***Velcade is an effective treatment for myeloma and that is clearly superior to Dexamethasone and the data supporting this is greater than for any other treatment for myeloma'.***

ii) ***The cost per QALY is less than £30,000'*****,** which falls within an acceptable range.

While I agree with these conclusions, the further interpretation of this is much more difficult to accept.

The ACD states that Velcade should only be available as part of a clinical trial. This effectively makes it impossible for patients with myeloma to receive this treatment and will undoubtedly impact in a very unfavourable fashion on the survival for these patents. There is currently no clinical trial, which is open for recruitment other than Myeloma IX, which is due to close in the near future. While conceptually it is correct to try to stimulate entry into clinical trials, in the

absence of any such trials, which are currently running and the long time period involved in setting up such trials, together with the lack of compulsion on individual Trusts to support the financial cost of trial drugs, the advice is currently inappropriate. In addition, there is a well-described syndrome of PCTs not wishing to prescribe Velcade unless it is in a clinical trial. If it is in a clinical trial, they do not want to fund it because it is research and the companies should fund it.

I would like to make a number of specific points:

i) Even at <£30,000 per QALY, the cost per QALY looks artificially high, not least because of the low cost Dexamethasone, but because it was not possible for the committee to consider the use of Velcade outside its licensed setting; this is inappropriate. It is very clear that the number of responses and outcomes are better when Velcade is combined with Dexamethasone, and if no response occurs within 3 cycles, it is possible to discontinue treatment. This decreases the cost per QALY further. A simple combination with oral alkylating agents such as Cyclophosphamide together with Dexamethasone can increase the response rates even further, and opens the possibility of longer disease free survival after cessation of treatment. This approach is clearly how the drug will be used in practice and a number of trials are currently looking at combinations such as this for presenting patients. There is a very sensible clinical rationale for making these simple combinations that has been worked out over the last 40 years of chemotherapy use. The response rate with combinations is very high, and patient's survival can be very long indeed. It is inappropriate to artificially set the rules such that this type of information cannot be accepted. There is a clear danger that with the pace of ongoing studies and with a large study of MP Velcade near to completion, that the NICE advice will seem ridiculously out of date.

ii) The treatment policy for first and second relapse of myeloma is actually clear and laid out in the BCSH guidelines:

   a. For older patients who may have received Melphalan and Prednisolone at presentation it would be appropriate to try the same treatment again if they have relapsed years after the initial exposure. If they failed to respond MP at presentation or relapsed early after first exposure, the use of Velcade would be highly appropriate.

   b. For younger patients autologous transplantation is the initial treatment of choice. If patients relapse early then Velcade may be appropriate. For patients who relapse after 18 months, a repeat autologous transplant, or Velcade would be appropriate. The cost comparison in this setting is very favourable.

iii) For patients with relapsed myeloma attaining a response is essential. Failure to obtain a response is followed by a rapid progression to

death. Thus in selecting the treatment for relapse there are a number of considerations. If a patient has been exposed to a drug before, they are likely to be resistant to it on subsequent exposure. The drug should be tolerable with few side effects, and give good responses. Any drug that gives a good response is likely to be effective clinically. Thus from a clinical perspective, randomised comparisons are perhaps not as relevant as may be thought to be in some quarters. We simply need to know what the prior treatment was, the performance status of the patient, the rate of responses, and duration of responses after they have been treated.

iv) It was implied in the meeting that although Dexamethasone was used in the Velcade trials, a more appropriate comparison was with Thalidomide. It is very difficult to consider Thalidomide as a comparator treatment for relapse. Much as the rules are set for the consideration of Velcade as a single agent, so they should be set for the consideration of Thalidomide. Thalidomide is highly effective at relapse, and is moving more into the first line setting, and it is likely most people will receive Thalidomide as part of the first line or maintenance treatment in the future. However, Thalidomide is not a licensed drug, and to consider it in the context of the ACD seems, therefore, inappropriate.

v) Conceptually stimulating entry into clinical trials is highly appropriate, especially for expensive novel agents. To state unequivocally though that Velcade can only be available for patients in clinical trials is highly inappropriate. As the Principle Investigator of the only trial that is using Velcade at relapse in the UK, it is important to say that the trial was not designed to address the question of how to use Velcade. However, that study will give further insight into the use of Velcade, how it should be sequenced, and the impact of prior treatments. It is not, however, a formal relapse trial. The study, Myeloma IX is due to close and no new patients will be able to be recruited into it within 6 to 12 months. As the median survival in the study is approaching 54 months, it will continue to recruit in the relapse setting. Patients who have not been entered into the study will not be eligible for treatment with Velcade.

The ACD advice is also ethically inappropriate even if a trial at relapse was set up, because of the necessity for equipoise in the trial design, any study would have to be an early versus late Velcade study. This is because it has clearly been demonstrated that Velcade is effective therapy at relapse.

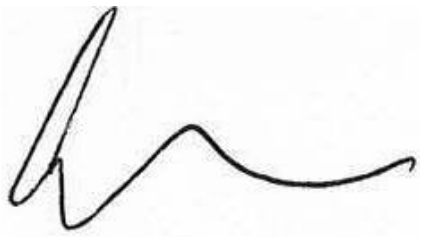
I felt that the appraisal was fair, and the results clear. That is that Velcade at relapse as a single agent is a more effective treatment than Dexamethasone as a single agent. The data supporting this conclusion is greater than it is for any other treatment at relapse. However, I feel the interpretation of this data is incorrect. There is clearly a place for Velcade in the treatment and relapsed and refractory myeloma. This does not have to be exclusively in the clinical trial setting. I applaud the Committee's desire to strengthen clinical trial entry.

However, I feel that in the setting of myeloma, it is highly inappropriate as it effectively means that patients in the UK will be denied a highly effective treatment, which can induce responses where they would not otherwise be obtained, and can thus prevent death from myeloma occurring. Trials should be developed to evaluate this drug for relapsed myeloma in the UK, however, these would take a minimum of 2-3 years to set up and even then, Trusts and PCTs may not support the additional drug costs.

My suggestion would be that Velcade was approved for relapsed myeloma and its use directed by the BCSH position statement on it. Appropriate trials should be initiated now. It should be recommended that Velcade is used in simple combinations and if responses are not attained, then it is appropriate to stop treatment.

With kind regards

Yours sincerely,



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