Appraisal Consultant Document (ACD)

Joint Patient Interest Group Submission

Bortezomib (Velcade) for Multiple Myeloma

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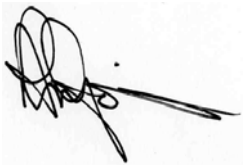

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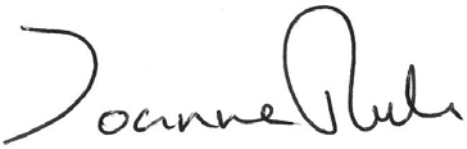

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Overview

IMF (UK), Leukaemia CARE, Leukaemia Research Fund and Cancerbackup believe that the length, and quality, of life for patients with myeloma will be reduced if NICE confirms the preliminary guidance in the ACD. We believe that no patient with myeloma should die without having access to bortezomib if it is what the treating physician, in consultation with the patient, believes is the appropriate therapy.

We welcome the opportunity to respond to the ACD and to provide further information and clarification to assist NICE in making an informed and positive final decision.

Jointly with the other stakeholders in the myeloma community we urge NICE to reconsider its position in light of the important points outlined in this response.

In summary, the decision does not appear to have fully considered the realities of clinical practice in myeloma, or the potential impact of its decision on patients for whom bortezomib is an important therapeutic option.

Summary of our response:

- Bortezomib should be approved as a treatment at first relapse, within its licensed indication, as per the Evidence Review Group's (ERG) findings and as per the BSCH position statement.

- In addition to the survival benefit, bortezomib is demonstrated to have no greater detrimental impact on quality of life than high-dose dexamethasone. Bortezomib showed a trend towards decreased number of grade 3 and greater infections, and prevented further bone destruction.

- Bortezomib can prolong the time to disease progression in patients with relapsed myeloma.

- Level one evidence from the APEX trial demonstrated that bortezomib is most clinically effective at first relapse, with respect to chance of response, time to disease progression and one-year survival.

- Bortezomib is most cost effective when used at first relapse, and introducing a stopping rule will avoid patients whose disease is not sensitive to proteasome inhibition being given unnecessary treatment and will reduce the cost per patient of treatment.

- Bortezomib offers a completely novel mode of action. It is therefore extremely important in treating patients, many of which are chemo resistant by the time they reach first relapse.

- The proposals in the draft guidance for further trials are neither practicable, nor ethical. The evidence in favour of bortezomib in relapsed patients is too strong to permit clinicians to randomise patients to receive alternative unproven treatments. Since the only drug licensed for this indication is high-dose dexamethasone, which

has been demonstrated inferior to bortezomib, trials testing this comparison are unethical. In addition, only around 10% of patients access trials.

- The failure to recommend the use of bortezomib is perverse and will leave patients without an effacious and licensed treatment option.

- Every patient, regardless of where they live or their individual circumstances should be entitled to receive those treatments recommended to them by their consultant, provided there is strong clinical evidence of their effectiveness. If, as NICE proposes, the only use of bortezomib should currently be in clinical trials, patients not eligible for trial participation but eligible under the licensed indication to receive the product would not be able to access it.

- Phase IV trials evaluating the true role of bortezomib in routine clinical practice should be implemented with appropriate funding provided by the Department of Health.

Living with multiple myeloma

An estimated 3,727[1] new cases of myeloma are diagnosed each year in England and Wales. The causes of myeloma remain unknown. Like most types of cancer, myeloma is more common in older people and it is unusual for myeloma to be diagnosed in people under the age of 50.

Myeloma is a disorder of the plasma cells. Blood cells are constantly generated. With myeloma, the production of new cells becomes out of control and large numbers of abnormal plasma cells are produced. These fill up the bone marrow and interfere with production of normal white cells, red cells and platelets. Several, or many, areas of bone may be affected. Myeloma causes thinning of the outer bone, fractures and pepper pot lesions in bone which are extremely painful.

The main symptom of myeloma is often back pain as it commonly affects the bones of the spine. Patients may also eperience loss of height. Other bones may also be affected such as the ribs, neck or pelvis. Other symptoms may include any of the following:

- excessive tiredness and lethargy due to a lack of red blood cells in the blood (*anaemia*)
- kidney problems caused by the paraproteins produced by the myeloma cells. Kidney damage can increase tiredness and anaemia
- repeated colds, coughs and other infections (particularly chest infections) because of a shortage of normal antibodies
- weakening of the bones by the myeloma cells, which may increase the risk of fractures
- loss of appetite, feeling sick, constipation, depression and drowsiness caused by too much calcium in the blood (*hypercalcaemia*). The excess calcium is released into the blood from the damaged bones
- unexplained bruising and abnormal bleeding (nosebleeds or bleeding gums) because the number of platelets in the blood has decreased

[1] CancerStats Monograph 2004, Cancer Research UK

- pins and needles, numbness, tingling or weakness in the feet or legs, difficulty passing urine or opening the bowels. Any of these symptoms could mean that a myeloma tumour is pressing on the spinal cord (known as *cord compression*).

Current treatment options for myeloma

Myeloma is rarely curable, but it is treatable, and treatment can be very effective at controlling symptoms and stopping the development of the disease.

Chemotherapy, usually combined with steroids, is the main treatment for myeloma. Many patients may benefit from high-dose chemotherapy. For this treatment, some of the blood stem-cells are removed, often from the blood but sometimes from the bone marrow, before the high-dose chemotherapy. They are given back through a drip after the high dose chemotherapy treatment. This is known as a stem-cell or bone marrow transplant and can help some people to stay in remission, but it is an intensive treatment that is not suitable for everyone.

After chemotherapy, interferon or steroids may be used to help keep the myeloma in remission.

Thalidomide although unlicensed, has in the last decade been found to be effective in controlling myeloma that has come back after chemotherapy. Thalidomide is also being tested as an initial treatment.

Drugs known as bisphosphonates are commonly used to reduce bone damage caused by the myeloma and to help bones to heal. They are also very helpful in lowering raised calcium levels in the blood. They can be given alongside chemotherapy or after chemotherapy has finished. They may also be given to help prevent bone damage from occurring.

Radiotherapy may be used to strengthen the bone and reduce pain in the affected areas.

Surgery may also occasionally be used to strengthen weakened bones, to prevent fractures or, rarely, remove areas of myeloma that are pressing on important areas of the body such as the spinal cord.

Bortezomib

Bortezomib is a new type of anti-cancer drug called a proteosome inhibitor. It is given to people who have already been treated with at least one other type of chemotherapy and who have already had, or are unsuitable for a bone marrow transplant, but whose myeloma has continued to develop.

Proteosomes are a group of enzymes found in all cells in the body. They have an important role in controlling cell function and growth. By interfering with the function of proteosomes, bortezomib may cause cancer cells to die and may stop the cancer from growing. Bortezomib is usually given intravenously, as four doses over a three-week period.

The APEX study was designed to confirm the efficacy and safety of bortezomib in patients who had previously received between one and three therapy treatments (not

bortezomib). Patients were randomly assigned to receive bortezomib or a standard high-dose treatment of dexamethasone.

Early results of the APEX study of 669 patients with relapsed or refractory myeloma dramatically favoured bortezomib and, in fact, the trial was halted early because of the distinct divergence between the bortezomib and dexamethasone arms. This study reported superior median time to progression, where time to progression was nearly twice as long in those taking bortezomib as against those taking dexamethasone (6.2 months versus 3.5 months for the dexamethasone group)[2].

More importantly in an update to the original report, the overall survival reported on the bortezomib arm was 29.8 months compared to 23.8 months despite 66% of the HDD patients being crossed over bortezomib, but being measured on the dexamethasone arm. This trial clearly showed that patients had an increased chance of response and prolonged survival at first relapse compared to later on in their disease.

In the update to the APEX study 43% of patients on this trial had a complete or partial response to bortezomib. The original trial reported a response rate of 18% to dexamethasone, which was not followed up in the update as most patients had crossed over to bortezomib at that point.

1. Whether you consider that all of the relevant evidence has been taken into account

We consider that some evidence has been either misinterpreted or misunderstood. Please consider the following additional points:

1.1 Patient Impact

The preliminary recommendation outlined in the ACD would have a serious detrimental impact on patients and their carers.

- Bortezomib has been demonstrated in randomised trials to offer an appreciable extension of time to progression and survival to patients with relapsed myeloma.

- The area of relapsed myeloma represents an area of unmet clinical need and failure to approve bortezomib will deprive myeloma patients of an effective therapy.

- In the absence of a formal QOFL assessment we believe note should be taken of the reduced number of serious adverse reactions, and a lesser degree of bone destruction with bortezomib should be highlighted.

- To restrict use of bortezomib to clinical trials will effectively render its availability to all NHS patients dependent on local policies of Primary Care Trusts; this is precisely the problem of "postcode prescribing" which was cited as one of the key reasons for establishing NICE.

[2] Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005; 352(24): 2487-98

- A decision not to recommend bortezomib would effectively mean that few patients will have access to this effective treatment, as fewer than 10% of patients ever get access to clinical trials.

1.2 Clinical Trials

The ACD indicates a recommendation for further trials and for bortezomib to be restricted to trial usage only. While we support the principle of testing new treatments in clinical trials, bortezomib has been shown to offer significant benefits over any other viable comparator. Further trials in this context are neither practicable, nor indeed ethical for the following reasons:

- APEX is the largest and most robust trial ever conducted in myeloma and constitutes level one evidence, which guides clinical practice with respect to sequencing of treatments.

- Following a pre-planned interim analysis of time to progression (TTP), the HDD arm of the APEX trial was halted early and all patients were offered bortezomib regardless of disease status. Because of the obvious improvement in response rates in the bortezomib wing of the study, it was considered unethical not to offer bortezomib to all participants.

- Both the ERG and the ACD acknowledge that bortezomib is clinically superior to high-dose dexamethasone (HDD) – which would make any further trial comparing bortezomib with HDD unethical.

- The evidence from APEX is already sufficiently strong to eliminate "therapeutic ambivalence" which is an ethical imperative to enter patients into randomised controlled trials.

- The recommendation that trials should be undertaken comparing bortezomib with current standard practice would not be feasible for the following reasons:

    - HDD is criticised in the ACD as a choice of comparator
    - We are not aware of any licensed treatment which would be eligible for use in a comparison arm of such a trial (thalidomide is not licensed for this indication)
    - Patients not eligible for trial participation, but eligible under the licensed indication to receive the product, would not be able to access it.

- We would anticipate that the standard of care by the time any possible trials would be reported will be to use both thalidomide and dexamethasone and cyclophosphamide as induction, negating their use in first relapse and rendering trials comparing bortezomib with these treatments of no clinical relevance.

- For the majority of patients, the revised MRC Myeloma IX protocol represents the only trial option in the next 2-3 years that incorporates bortezomib. Many Trusts/Networks have blocked access to this trial because of the perceived costs of the treatment options and because of the operational costs associated with analysing and reporting data. Current evidence strongly suggests that less than 10% of the myeloma community will be entered into this trial.

- The MRC IX trial was not designed to answer scientific questions on where best to use bortezomib – the bortezomib sub-protocol amendments will only answer questions on the impact of treating patients previously treated with thalidomide or not. The relapsed protocol is not randomised, or compulsory, and is therefore not relevant.

- Initiating a major, new clinical trial is an enormously time-consuming and bureaucratic process - from outline to first entry of patients would be 18-24 months at best – and may be impossible if funding and a sponsor cannot be obtained. During the trial development process under the proposals set out in the ACD, the majority of patients would go without a licensed treatment option. Furthermore, for the reasons stated above, it is likely that such a trial would be refused ethical approval and, if approved, it is likely that many clinicians would refuse on ethical grounds to enrol patients.

- A further difficulty with designing and interpreting any such trials is the high probability that, by the time any trial is completed, immunomodulatory drugs (IMiD's) will be entering wider clinical use and the comparisons would be out of date. The trials would then be subject to the same criticisms as are made in the current ACD concerning the use of HDD as a comparator arm. Bortezomib should be available as a treatment option in order to progress clinical trials over the next five years and arguably it should become the standard comparator for future trials.

To restrict the use of bortezomib to clinical trials will therefore effectively render its availability to all NHS patients dependent on local policies of Primary Care Trusts; this is precisely the problem of "postcode prescribing" which was cited as one of the key reasons for establishing NICE.

2. Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate…

2.1 Cost Effectiveness factors

There are a number of points we urge NICE to consider:

- The health outcomes data in the manufacturer's submission and the ACD did not take into account a stopping rule at three cycles in non-responding patients. Introducing such a stopping rule would significantly reduce the cost/QALY.

- The health outcomes data in the manufacturer's submission and the ACD did not take into account the addition of dexamethasone. This would reduce the cost per QALY. The ERG recognised that the addition of HDD improved cost effectiveness and although bortezomib is only licensed as mono-therapy, it is, in practice, most widely used in combination (and HDD is referred to in the SPC).

- The extremely low cost of HDD compared to other possible treatments artificially inflates both the ICER and the comparative cost per QALY. NICE must be able to consider comparisons of expensive new treatments with older, cheaper, treatments in a more meaningful way.

- When compared with the cost of an autologous transplant - which is noted in the ACD as a potential treatment for myeloma at first relapse, the cost of a single course of bortezomib is significantly lower.

- As new treatments are incorporated into practice and clinicians become better able to manage their side effect profiles, associated quality of life for patients improves. This will have a favourable impact on cost per QALY and NICE should consider the lifetime of a drug rather than the first use in clinical trials.

- The rigid applicability of a maximum QALY of £30,000 to this appraisal is questionable. We would expect NICE to accommodate a new drug in an uncommon cancer in a similar way to which it would deal with a treatment for an orphan disorder.

2.2 Comparator of HD Dexamethasone (HDD)

The ACD criticises the choice of HDD as a comparator – at the time the trial was initiated this was the only licensed drug for myeloma and therefore the only one appropriate for a registration trial. HDD is used by a number of international study groups including SWOG and ECOG as a comparator in the field of myeloma. Other new therapeutic agents indicated for myeloma will also use HDD as a comparator.

2.3 Clinical Audit

We have already made the case that the trials that are recommended in the draft guidance are neither practicable, nor ethical. We believe that there is a strong case to recommend making the drug available with an accompanying requirement that there should be ongoing data collection and review of cost-effectiveness.

3. Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS…

3.1 Objections to initial recommendation

In myeloma, there are a variety of bespoke pathways to accommodate the heterogenous nature of the disease in patients with this complex, debilitating cancer. We believe that the appraisal committee has not fully understood the reason for the more complex treatment pathways for this group of patients.

For all the reasons outlined above, the ACD does not reflect the best interests of patients and their carers and does not take appropriate account of all the available evidence.

4. Declarations of Interest

- Cancerbackup has received sponsorship for several publications and projects from Ortho Biotech, the manufacturer of bortezomib.

- IMF (UK) receives an unrestricted educational grant from Ortho Biotech to use across its range of services
- Leukaemia CARE has received an unrestricted educational grant from Ortho Biotech towards the running costs of our Patient Conferences, and we also receive a regular supply of unbranded patient information leaflets on Cancer related Fatigue, Work and Cancer, and Understanding Myeloma.

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