

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## GUIDANCE EXECUTIVE (GE)

### Review of TA129; Bortezomib monotherapy for relapsed multiple myeloma and TA171; Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy

TA129 was issued in October 2007 and TA171 in June 2009.

A decision was made by the Institute's Guidance Executive in October 2010 to defer the review date for both pieces of guidance to mid-2011. This was subsequently deferred to the present date in order to allow discussions to take place with the Department of Health regarding the patient access schemes relating to both these technologies.

#### 1. Recommendation

Both pieces of guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

#### 2. Original remit(s)

TA129: *"To prepare a technology appraisal on the clinical and cost effectiveness of bortezomib within its licensed indications for the treatment of relapsed and refractory multiple myeloma"*.

TA171: *"To appraise the clinical and cost effectiveness of lenalidomide in combination with dexamethasone for the treatment of multiple myeloma in people who have received at least one prior therapy"*.

#### 3. Current guidance

##### TA129

- 1.1. Bortezomib monotherapy is recommended as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation, under the following circumstances:
  - the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a complete or partial response (that is, reduction in serum M protein of 50% or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response) **and**

- the manufacturer rebates the full cost of bortezomib for people who, after a maximum of four cycles of treatment, have less than a partial response (as defined above).
- 1.2. People currently receiving bortezomib monotherapy who do not meet the criteria in paragraph 1.1 should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

## **TA171**

- 1.1. Lenalidomide in combination with dexamethasone is recommended, within its licensed indication, as an option for the treatment of multiple myeloma only in people who have received two or more prior therapies, with the following condition:
- the drug cost of lenalidomide (excluding any related costs) for people who remain on treatment for more than 26 cycles (each of 28 days; normally a period of 2 years) will be met by the manufacturer.
- 1.2. People currently receiving lenalidomide for the treatment of multiple myeloma, but who have not received two or more prior therapies, should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

## **4. Rationale<sup>1</sup>**

The literature search did not identify any new published clinical evidence which is likely to lead to a change in the recommendations in previous guidance. No changes to existing patient access schemes are currently proposed and no other guidance is in development.

## **5. Implications for other guidance producing programmes**

None identified.

## **6. New evidence**

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from February 2006 (TA129) and March 2008 (TA171) onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. No ongoing trials relating to these appraisals were found.

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<sup>1</sup> A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

## 7. Summary of evidence and implications for review

Since the previous guidance was issued, no new interventions have come to market.

### TA129 (bortezomib):

The marketing authorisation of bortezomib has been extended to include use in combination with melphalan and prednisone, for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant. This indication was appraised in NICE TA 228, July 2011 (due for review July 2014).



The updated literature searches identified results of a randomised controlled trial comparing subcutaneous bortezomib therapy to intravenous therapy in adults with relapsed multiple myeloma who had received one to three previous lines of therapy (Moreau et al. 2011). The results demonstrated that subcutaneous bortezomib offers similar efficacy to standard intravenous administration, with an improved safety profile. Subcutaneous administration of bortezomib (if licensed) could reduce the administration cost and may affect the original ICER. A sensitivity analyses in the original manufacturers submission showed that the ICER was not very sensitive to drug administration costs, but it is expected that having reduced administration costs would decrease the ICER slightly and therefore not lead to change in the recommendations made in TA129.

A post hoc analysis evaluating the efficacy of dexamethasone addition to bortezomib in patients with relapsed and/or refractory multiple myeloma who had a suboptimal response to bortezomib alone in the two phase 2 studies, reported improvement in responses without any prohibitive toxicity (Jagannath et al., 2006).

A large (n=646) phase III multicentre, open-label, randomized trial comparing pegylated liposomal doxorubicin (PLD) plus bortezomib with bortezomib monotherapy in patients with relapsed or refractory multiple myeloma showed that PLD with bortezomib is superior to bortezomib monotherapy for the treatment of patients with relapsed or refractory multiple myeloma. However, the combination therapy is associated with a higher incidence of grade 3 or 4 myelosuppression, constitutional symptoms, and GI and dermatologic toxicities.

PLD has been granted marketing authorisation for the treatment of progressive multiple myeloma in combination with bortezomib, in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant. This topic had been evaluated as part of the topic selection

process between July 2006 and December 2008 (wave 15-21) and was not considered a priority according to Department of Health selection criteria and had been excluded from the process prior to being evaluated by a topic selection panel.

One small (n=32) prospective single arm study reported bortezomib retreatment in patient with multiple myeloma who had previously responded to bortezomib (Sood et al., 2009). The study evaluated the response rate in patients who had at least a partial response (PR) on initial bortezomib therapy. Patients were allowed to receive bortezomib alone or in combination with dexamethasone, thalidomide, or doxorubicin and the authors concluded that retreatment with bortezomib alone or in combination is effective and well tolerated in patients who have responded to their initial bortezomib treatment.

The searches also identified a cost-effectiveness study, comparing bortezomib with dexamethasone as a second-line treatment of relapsed/refractory multiple myeloma using survival data of the APEX trial (bortezomib vs. dexamethasone). This study also attempted a comparison of bortezomib with lenalidomide, by using data from the MM-09/10 which compared lenalidomide plus dexamethasone with dexamethasone alone. This comparison appears not to be done by a formal adjusted indirect comparison, and indicated that bortezomib may be associated with better outcomes than lenalidomide.

#### **TA 171 (lenalidomide):**

The marketing authorisation for lenalidomide has not changed and Celgene, the manufacturer of lenalidomide have confirmed that no extension to the existing marketing authorisation is expected in the relapsed refractory setting.

Celgene

[REDACTED]

and appraisals for these indications are currently in progress.

Celgene also indicated the willingness to continue with the current patient access scheme without any change. Celgene also stated that data on uptake of the scheme is being collected and it may take another 2-3 years for an accurate analysis of saving to the NHS.

A cost-effectiveness study comparing lenalidomide plus dexamethasone with dexamethasone alone in relapsed/refractory multiple myeloma using efficacy data of a subgroup from the MM-009/010 trials demonstrated that lenalidomide is a cost-effective option for patients whose disease has relapsed after treatment with bortezomib.

In a post hoc analysis of data from the MM-009 and MM-010 trials the outcome of a subset of patients who had received lenalidomide plus dexamethasone after only one prior therapy was compared to outcomes for patients treated in later stage. The result showed that patients with one prior therapy showed a significant improvement

in benefit after first relapse compared with those who received two or more therapies (Stadtmauer et al. 2011).

The prices of lenalidomide and bortezomib have not changed since the issue of guidance.

## **8. Implementation**

A submission from Implementation is included in Appendix 3.

Data calculated by IMS that indicated that the volume of prescribing of bortezomib and lenalidomide increased in the months following the publication of TA129 and TA171. However, these data do not link to diagnosis and so should be treated with caution.

A survey published in 2009 concluded that nearly two thirds of Primary Care Trusts and just over a third of Local Health Boards indicated that they funded bortezomib and lenalidomide routinely.

## **9. Equality issues**

No equality issues were identified.

**GE paper sign off:** Elisabeth George, 16 Feb 2012

### **Contributors to this paper:**

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## Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – ‘Yes/No’
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE’s work programme.	No
The decision to review the guidance should be deferred (to a specified date).	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	<p>The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review.</p> <p>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.</p>	No. There are no related clinical guidelines.
The guidance should be updated in an on-going clinical guideline.	<p>Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn.</p> <p>Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).</p>	No. There are no related clinical guidelines.

Options	Consequence	Selected – ‘Yes/No’
<p><b>The guidance should be transferred to the ‘static guidance list’.</b></p>	<p>The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.</p>	<p>Yes. There is no current evidence which would change the recommendation in the existing appraisal. This decision may be revisited should the details of the current access scheme be revised.</p>

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

- i. The technology falls within the scope of a clinical guideline (or public health guidance)
- ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement
- iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment
- iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;
  - Spending on a treatment for the indication which was the subject of the appraisal continues to rise
  - There is evidence of unjustified variation across the country in access to a treatment

- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
  - The treatment is excluded from the Payment by Results tariff
- v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

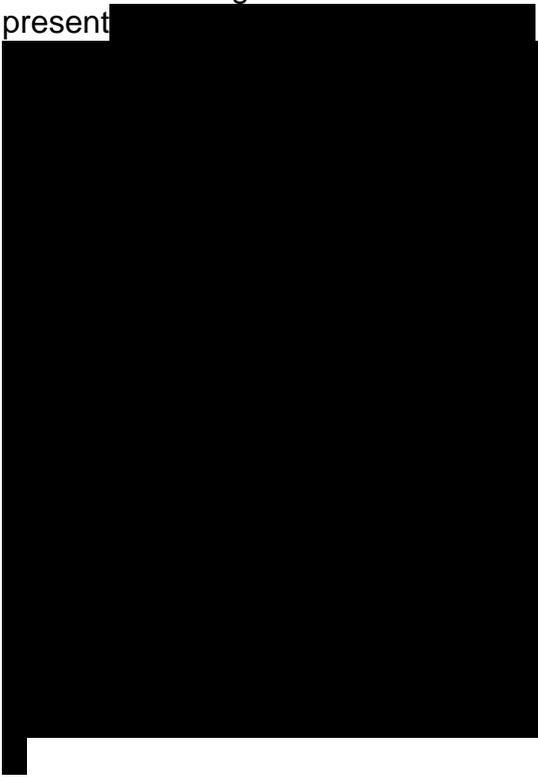
## Appendix 2 – supporting information

### Relevant Institute work

*In progress*

Vorinostat in combination with bortezomib for the treatment of multiple myeloma in people who have received at least one prior therapy. Technology Appraisal. Expected: October 2013.

### Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
<p>Bortezomib:</p> <p><i>“monotherapy for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation”.</i></p>	<p>The indication for this appraisal remains unchanged at present</p> 
<p>Lenalidomide:</p> <p><i>“in combination with dexamethasone for the treatment of multiple myeloma in patients who have received at least one prior therapy”.</i></p>	<p>No change to the indication for this appraisal.</p> <p>Technology Appraisals on lenalidomide for first line/maintenance treatment of multiple myeloma are also on the NICE work programme.</p>

**Details of new products** (note: information in this section is sourced from the New Drugs Online database unless otherwise stated)

<b>Drug (manufacturer)</b>	<b>Details (phase of development, expected launch date, )</b>
Bortezomib (subcutaneous preparation) (Janssen Cilag)	Results from a phase III study in relapsed multiple myeloma were published online in April 2011. UK launch anticipated in 2012.
Carfilzomib (Onyx)	Phase III for patients with advanced, refractory myeloma. UK launch anticipated ~2013.
Elotuzumab (Bristol Myers Squibb)	Phase III in combination with lenalidomide/dexamethasone for relapsed or refractory multiple myeloma. Trial is not due for completion until 2017.
Enzastaurin (Eli Lilly)	Phase II, UK launch estimated to be ~Q1 2016.
Mapatumumab (Human Genome Sciences)	Phase II study (in combination with bortezomib for relapsed or refractory multiple myeloma) completed. UK launch anticipated ~2015.
Milatuzumab (Immuno Medics US )	Phase II for relapsed multiple myeloma.
Natalizumab (Elan)	Phase II for relapsed or refractory multiple myeloma. UK launch anticipated ~2016.
Panobinostat (Novartis)	Phase III for previously treated multiple myeloma whose disease has recurred or progressed. Regulatory filings planned for 2013..
Pegylated liposomal doxorubicin hydrochloride (Janssen Cilag)	Licensed in combination with bortezomib for progressive multiple myeloma in patients who have received at least one prior therapy and who have undergone or are unsuitable for bone-marrow transplantation.
Perifosine (Keryx)	Phase III for relapsed/refractory multiple myeloma. UK launch

Drug (manufacturer)	Details (phase of development, expected launch date, )
	anticipated ~2013.
Plitidepsin (PharmaMar)	Phase III for relapsed/refractory multiple myeloma. UK launch anticipated ~2015.
Pomalidomide (Celgene)	Phase III, UK launch anticipated ~2016.
Siltuximab (Centocor)	Phase III trial (in combination with bortezomib and dexamethasone) currently being planned.
Tanespimycin (Bristol Myers Squibb)	Phase II/III in combination with bortezomib for relapsed/refractory multiple myeloma following the failure of at least three prior anticancer therapy regimens (which must have included bortezomib and lenalidomide).
Vorinostat (Merck)	Phase III in combination with bortezomib for relapsed/refractory multiple myeloma. 

### Registered and unpublished trials

No relevant RCTs found.

### References

Moreau P, Pylypenko H, Grosicki S et al. (May 2011) Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study.[Erratum appears in Lancet Oncol. 2011 Jun;12(6):522]. Lancet Oncology 12 (5): 431-440.

Jiang Y, Spencer M, Gauthier A et al. (2011) A cost-effectiveness analysis for second-line treatment of relapsed/refractory (RR) multiple myeloma (MM) in the United Kingdom. Value in Health Conference: ISPOR 14th Annual European Congress Madrid Spain. Conference Start: 20111105 Conference End: 20111108. Conference Publication: (var.pagings): A452-.

Schey S, Stern S, Dhanasari S, et al. (2011) Cost-effectiveness of Lenalidomide in Multiple Myeloma Patients with 1 Prior Therapy in England and Wales. Poster presented at the 53<sup>rd</sup> Annual Meeting of the American Society of Hematology, December 10-13, 2011 San Diego, CA, Abstract#418

Stadtmauer EA, Weber DM, Niesvizky R et al. (2009) Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. *European journal of haematology* 82 (6): 426-432.

San-Miguel JF, Dimopoulos MA, Stadtmauer EA et al. (Feb. 2011) Effects of lenalidomide and dexamethasone treatment duration on survival in patients with relapsed or refractory multiple myeloma treated with lenalidomide and dexamethasone. *Clinical lymphoma, myeloma & leukemia* 11 (1): 38-43.

Jagannath S, Richardson PG, Barlogie B, et al: Bortezomib in combination with dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma with less than optimal response to bortezomib alone. *Haematologica* 91:929-934, 2006.

Orlowski RZ, Nagler A, Sonneveld P, et al.(2007) Randomized Phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: Combination therapy improves time to progression. *J Clin Oncol* 25:3892–3901

Bladé J, Sonneveld P, San Miguel JF, et al.(2008) Pegylated liposomal doxorubicin plus bortezomib in relapsed or refractory multiple myeloma: efficacy and safety in patients with renal function impairment. *Clin Lymphoma Myeloma* 8(6):352–355.

Sood, R., Carloss, H., Kerr, R., Lopez, J., Lee, M., Druck, M., Walters, I. B. and Noga, S. J. (2009), Retreatment with bortezomib alone or in combination for patients with multiple myeloma following an initial response to bortezomib. *American Journal of Hematology*, 84: 657–660

## **Appendix 3 – Implementation submission**

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**IMPLEMENTATION DIRECTORATE**

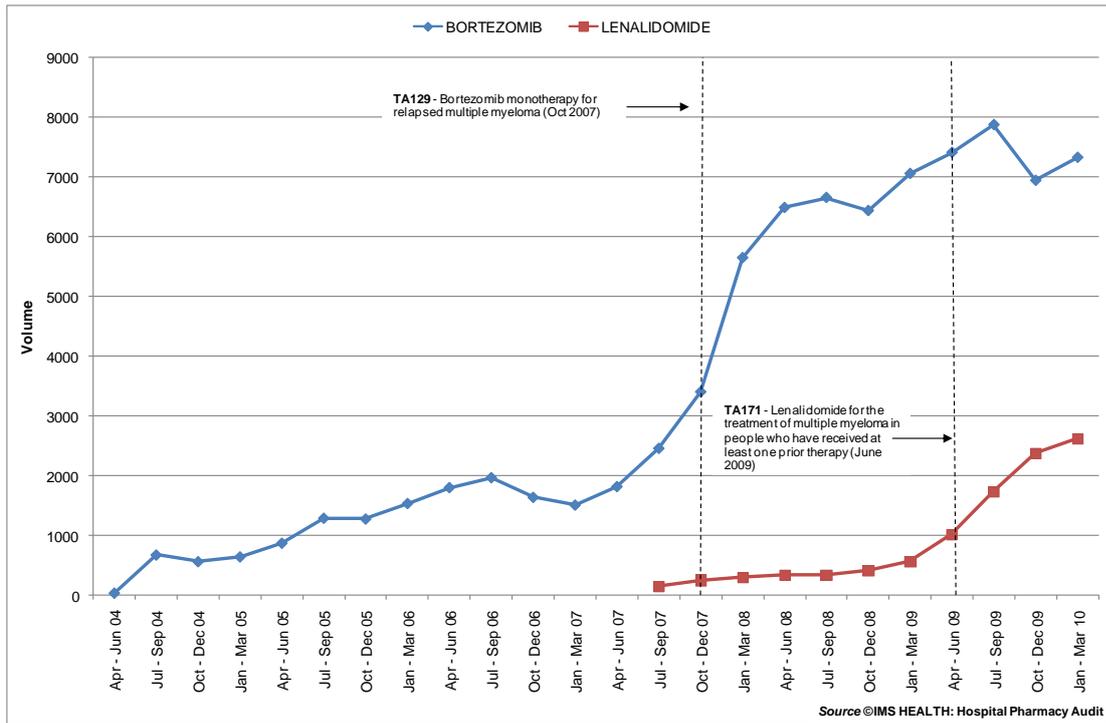
**Guidance Executive Review**

**Technology appraisal 129 & 171: Bortezomib monotherapy for relapsed multiple myeloma and lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy**

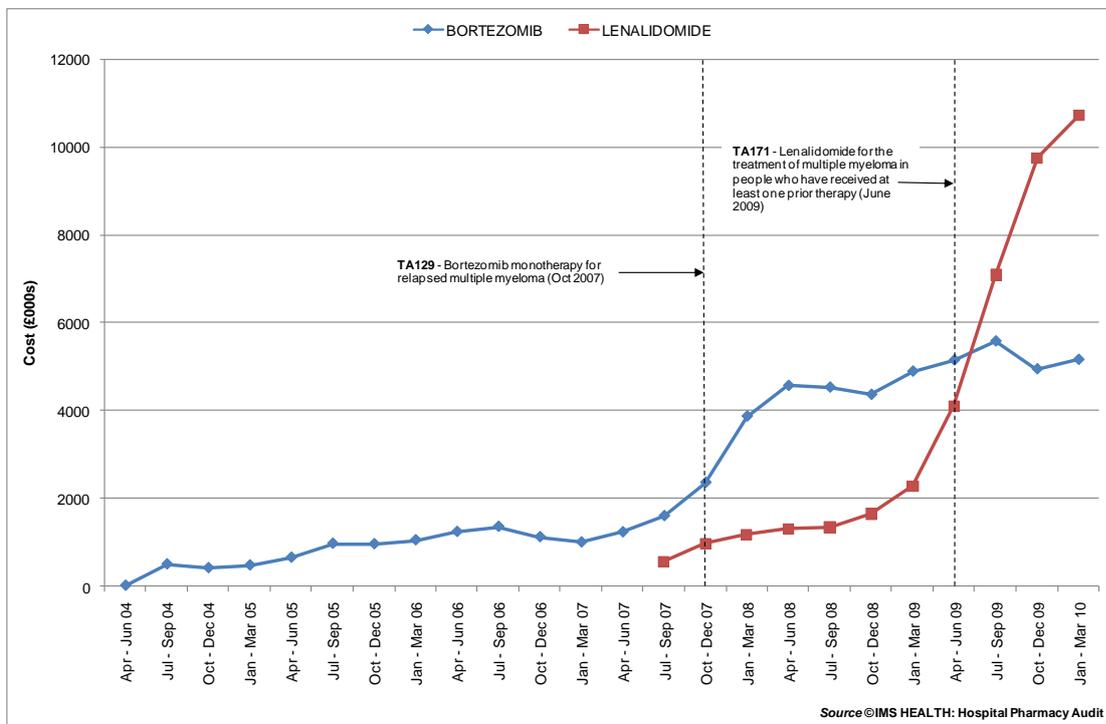
### **1. Routine healthcare activity**

Data showing trends in prescribing costs are presented below. Unfortunately this data does not link to diagnosis so needs to be treated cautiously in relation to the specific recommendations of the guidance. Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

**Figure 1 Trend in volume of prescribing of bortezomib and lenalidomide in hospitals in England**



**Figure 2 Trend in cost of prescribing of bortezomib and lenalidomide in hospitals in England**



The estimated cost for bortezomib and lenalidomide in hospitals in England in the first quarter of 2010 was £5,162,234 and £10,712,475 respectively.

Notes:

- The IMS HEALTH Hospital Pharmacy Audit Index (IMS HPAI) collects information from pharmacies in hospital trusts in the UK. The IMS HPAI database is based on 'issues' of medicines recorded on hospital pharmacy systems. 'Issues' refer to all medicines supplied from hospital pharmacies to: wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.
- Volume/Quantity: This is the number of packs of a medicine that are issued. They should not be added together due to differences in dosages/pack sizes.
- Cost (in £s): Estimated costs are calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost. Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The estimated costs are used as a proxy for utilization and are not suitable for financial planning.
- Ideally data would show the total number of patients prescribed a medicine and the volume and duration of treatment. However, the current datasets do not facilitate this type of analysis. Cost and volume therefore need to be considered together to provide the closest approximation. Cost provides a more accurate view of the total amount of a medicine dispensed. However, it does not provide an indication of the number of patients prescribed a medicine. Volume therefore provides an indication of the number of packs used, although it does not account for patients receiving different dosages or durations.
- Unfortunately this data does not link to diagnosis so needs to be treated cautiously in relation to the specific recommendations of the guidance.

## 2. Implementation studies from published literature

### 2. External literature

#### 2.1 Leukaemia Care (2009) [2009 Haematology Survey](#)

A survey examining the extent to which NICE guidance (bortezomib and rituximab) is being implemented, and how and when PCTs are making treatments available to patients in England and Wales. The study found that only 60% of PCTs and 35% of LHBs said they fund these treatments routinely