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Janssen's Response to the Appraisal Consultation Document

Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy with bortezomib (partial review of TA171)

Please find below Janssen's response to the Appraisal Consultation Document (ACD) for the partial review of TA171. We are pleased to have the opportunity to provide our comments in relation to the interpretation of the cost-effectiveness evidence within the ACD and these are detailed below.

We would like to provide further information which should be taken into account before making a final recommendation.

Our response to the ACD will be addressed in section 1 where we highlight our response with respect to the evidence base used in this appraisal. Specifically the route of administration with bortezomib, duration of treatment with bortezomib and treatment administration costs. We do not have any comments for sections 2-4.

We also want to address the description of the bortezomib response scheme in the ACD (section 3.19): *"Although patient access schemes (discounts) are available for bortezomib after 1 prior therapy and lenalidomide after 2 prior therapies, the manufacturer did not include these in the model base case".* As the bortezomib response scheme is a response-based, complex financial patient access scheme and not a simple discount off the list price, we are concerned that the text contained within the ACD implies otherwise. As such, it is inaccurate for the Committee to refer to the bortezomib response scheme in terms of "discount" and may be understood as an endorsement of the figure as a discount off the list price and used as actual discount figures by third parties. We therefore request that the Committee refrain from referring to the bortezomib response scheme as a "discount" patient access scheme in future documentation for this appraisal.

We propose that the final guidance should incorporate the additional information and uncertainty we present below to ensure that the evidence base is accurately reflected.

Section 1: Has all of the relevant evidence been taken into account?

1.1 *Assumptions made by the manufacturer about the route of administration with bortezomib*

Throughout the manufacturer's submission the administration of bortezomib is referred to as being intravenous (IV). Consequently, administration costs are calculated based on IV administration. We would like to point out that as of September 2012, bortezomib has a licence for subcutaneous (SC) administration[1]. The SC formulation should therefore be used when the administration cost for bortezomib is calculated in the model and it should be borne in mind that the SC administration route also allows patients to attend hospital as day cases in an outpatient setting.

Additionally, we would like to point out that although the manufacturer accurately represents the adverse event results from the VISTA trial, bortezomib was administered IV in that trial. As stated in the Summary of Product Characteristics (SPC), a Phase III study comparing bortezomib administered IV versus SC, the incidence of Grade ≥ 2 peripheral neuropathy events were statistically significantly lower for the SC injection group than for the IV injection group (24% vs. 41%; p=0.0124). Similarly, grade ≥ 3 peripheral neuropathy occurred in statistically significantly fewer patients in the SC treatment group, compared to the IV treatment group (6% vs. 16%; p=0.0264)[1]. It is therefore likely that the rates of peripheral neuropathy will be lower than that used in the model to determine costs associated with treating this adverse event in the bortezomib group.

Janssen is concerned that a number of incorrect assumptions were made in the manufacturer's submission about the route of administration for bortezomib and subsequent costs. This has the consequence of increasing the cost associated with bortezomib use, thereby underestimating the ICER for lenalidomide compared with bortezomib. Janssen requests that the cost of SC administration be taken into consideration when calculating the cost of bortezomib.

1.2 Assumptions made by the manufacturer about cost in relation to lenalidomide administration.

We would like to point out that the assumption regarding administration costs for lenalidomide in the manufacturers' submission as once-off costs is incorrect. The chemotherapy regimen clinical coding guidance OPCS-4.6[2] states that the delivery code *"…must be assigned to the attendance where the patient is given the drug(s) to take home and receives counselling and advice on taking the drug at home by a responsible consultant, a pharmacist or a specialist chemotherapy practitioner, this will usually be within the oncology unit. Oral chemotherapy regimen prescriptions may be given to a patient for a*

period of up to three months before the patient needs to be reviewed." This implies that any attendance to the patient following treatment review has an associated cost.

The manufacturer's submission states that the MM010 study protocol allowed for lenalidomide treatment interruptions and subsequent dose reductions, which were accounted for in the model. It is therefore reasonable to assume that patients would have been attended to by a consultant, pharmacist or specialist chemotherapy practitioner to receive advice on taking the drug at a different dose or discontinuing the drug. Thus it would be a more accurate reflection of lenalidomide administration costs to incorporate the costs of subsequent visits for dose reductions or dose interruptions. We suggest that the cost of lenalidomide administration be adjusted accordingly.

Janssen is concerned that incorrect assumptions were made in the manufacturer's submission about the route of administration for lenalidomide. This has the consequence of underestimating the cost associated with lenalidomide use and underestimating the ICER for lenalidomide compared with bortezomib. Janssen requests that the administration cost of subsequent visits for dose adjustment or interruption with lenalidomide be taken into consideration in determining the base-case ICER.

1.3 Assumptions made by the manufacturer about the number of cycles in the relapse setting

Further to the ERG's clinical specialist's suggestion that bortezomib in the UK is given for a fixed number of cycles (and not until disease progression as assumed by the manufacturer), we would like to emphasize the information presented in the bortezomib SPC. The SPC states that the maximum recommended number of cycles with bortezomib in combination with dexamethasone in progressive myeloma (patients who have received one prior therapy) is 8[1]. It is also recommended that for monotherapy in the same setting, patients receive 2 cycles of bortezomib following a confirmation of a complete response and responding patients who do not achieve a complete remission receive a total of 8 cycles of bortezomib therapy[1].

Janssen is concerned that an incorrect assumption on duration of second line therapy with bortezomib in the manufacturer's submission has been used. This has the consequence of increasing the cost associated with bortezomib use in the model, thereby underestimating the ICER for lenalidomide compared with bortezomib. Janssen requests that the cost of using the recommended number of cycles as per the SPC, be taken in to consideration in determining the base-case ICER.

1.4 Assumptions made by the manufacturer about the evidence base for the population under consideration

We agree with the Appraisal Committee considerations around the population in the lenalidomide MM-009 and MM-010 trial, which does not match the population set out in the scope for the appraisal. To our knowledge, there is no robust evidence to support the assumption that prior bortezomib therapy would not affect the efficacy profile of subsequent treatment with lenalidomide. Therefore the Hazard Ratio obtained from the comparison of the lenalidomide (MM-010) and bortezomib (Taverna et al.) studies should be interpreted with caution.

Janssen is concerned that there is a lack of robust evidence comparing lenalidomide and bortezomib in the population under consideration. This contributes to the uncertainty around the cost-effectiveness analysis and Janssen requests that careful consideration should be taken when evaluating the comparative effectiveness of lenalidomide and bortezomib.

Section 2: Are the summaries for clinical and cost-effectiveness reasonable interpretations of the evidence?

No further comments.

Section 3: Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

No further comments.

Section 4: Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No further comments.

Reference List

1. Janssen-Cilag Ltd. Velcade 3.5mg powder for solution for injection.Summary of Product Characteristics. Electronic Medicines Compendium. 2013. 19-12-2013.
Ref Type: Electronic Citation

2. Swain,L. Chemotherapy Regimens Clinical Coding Guidance - OPCS-4.6 (April 2013-14). Health & Social Care Information Centre. [Version 3.1], 1-21. 2013. Crown Copyright.
Ref Type: Electronic Citation