

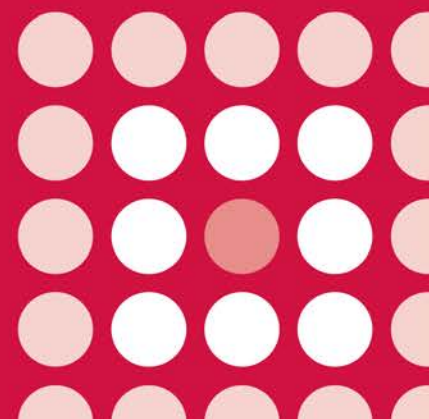
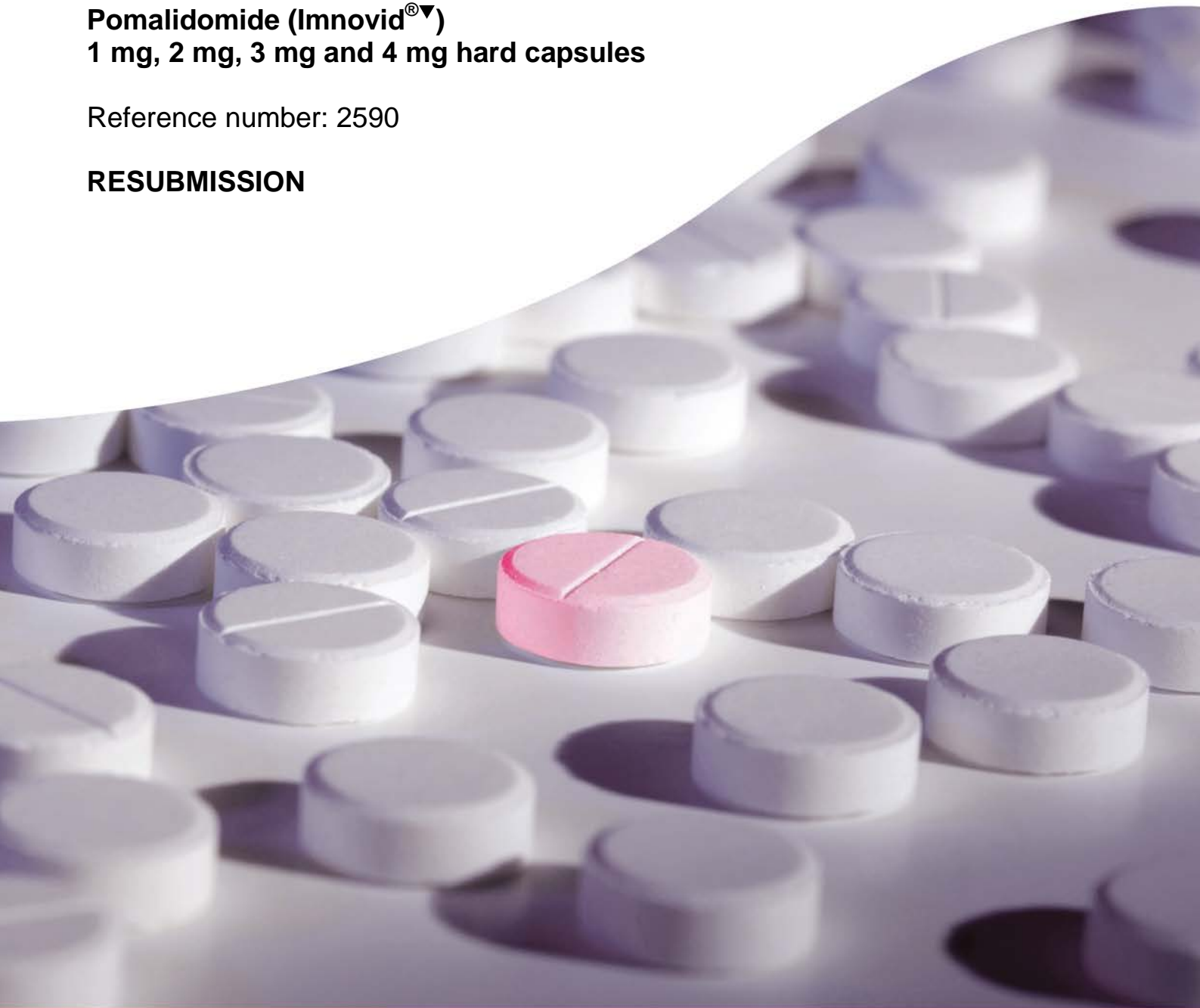


AWMSG SECRETARIAT ASSESSMENT REPORT

Pomalidomide (Imnovid[®]▼)
1 mg, 2 mg, 3 mg and 4 mg hard capsules

Reference number: 2590

RESUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report
Pomalidomide (Imnovid[®]▼)
1 mg, 2 mg, 3 mg and 4 mg hard capsules

This assessment report is based on evidence submitted by Celgene Ltd. on 31 October 2014¹.

1.0 PRODUCT DETAILS

Licensed indication under consideration	Pomalidomide (Imnovid [®] ▼) in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy ² .
Dosing	The recommended starting dose of pomalidomide (Imnovid [®] ▼) is 4 mg once daily taken orally on Days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle. Dosing is continued or modified based upon clinical and laboratory findings. Treatment should be discontinued upon progression of disease. Refer to the summary of product characteristics (SPC) for information on dose modification or interruption ² .
Marketing authorisation date	5 August 2013 ²

2.0 DECISION CONTEXT

2.1 Background

Multiple myeloma is a cancer arising from the accumulation of abnormal plasma cells (myeloma cells) in the bone marrow, affecting the production of normal blood cells³. The clinical presentation is varied, but symptomatic multiple myeloma (signalling the necessity for treatment) is typified by hypercalcaemia, renal insufficiency, anaemia and bone lesions⁴. It accounts for 1% of all cancers and approximately 10% of all haematological malignancies^{4,5}. There were 228 new cases of myeloma diagnosed in 2011 in Wales and the age-standardised incidence was 4.6 per 100,000⁶. Patients diagnosed with multiple myeloma tend to be older, with 71% of people in England and Wales diagnosed at age 65 years and over³.

Multiple myeloma remains an incurable, terminal disease with an average survival of four to six years³. The typical disease course is characterised by a chronic phase lasting several years and an aggressive terminal phase⁴. Following initial treatment most patients will usually experience a period of remission but all relapse eventually³. Bortezomib and lenalidomide-based regimens are the most commonly used agents for relapsed or refractory multiple myeloma and are recommended by national guidelines^{4,7-9}. Very few options remain for patients who have already tried the standard treatments for multiple myeloma^{3,4}. Options that might be considered are palliation, a second autologous stem cell transplant (ASCT), re-challenge with a previously effective treatment or enrolment in a clinical trial. However, outcomes are generally poor, with short response durations and increasing medicine resistance³.

Pomalidomide is an immunomodulatory agent licensed for relapsed and refractory multiple myeloma in patients who have received two previous treatments, including both lenalidomide and bortezomib, and have demonstrated disease progression². It is a structural analogue of lenalidomide and thalidomide, but is not considered to be a derivative of either⁴. The exact mechanism of action is unknown, but pomalidomide has the tumouricidal, immunomodulatory, anti-angiogenic and anti-inflammatory properties seen with other medicines in this class^{1,3,4}.

The All Wales Medicines Strategy Group (AWMSG) has previously assessed and not recommended the use of pomalidomide for the indication under consideration¹⁰. An updated AWMSG application has been made for pomalidomide, which includes a Wales Patient Access Scheme (WPAS)¹.

2.2 Comparators

The comparators included in the company submission were:

- Retreatment with bortezomib (Velcade[®]) + dexamethasone
- Bendamustine hydrochloride (Levact[®]) + thalidomide (Thalidomide Celgene[®]) + dexamethasone
- Bendamustine hydrochloride (Levact[®]) + prednisolone

2.3 Guidance and related advice

- NICE Technology appraisal guidance (TA338). Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib (2015)¹¹.
- The British Committee for Standards in Haematology (BCSH) Guidelines for the diagnosis and management of multiple myeloma (2014)⁷.
- NICE Technology appraisal guidance (TA311). Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (2014)¹².
- Multiple myeloma: European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment and follow-up (2013)⁵.
- NICE Technology appraisal guidance (TA228). Bortezomib and thalidomide for the first-line treatment of multiple myeloma (2011)¹³.
- NICE Technology appraisal guidance (TA171). Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (2009)⁹.
- NICE Technology appraisal guidance (TA129). Bortezomib monotherapy for relapsed multiple myeloma (2007)⁸.

AWMSG has previously issued a non-recommendation for the use of pomalidomide (Imnovid[®])¹⁰.

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The main clinical evidence provided by the applicant company was from the phase III pivotal study CC-4047-MM-003 (MM-003)¹⁴. In addition, the company conducted a systematic literature review to identify comparator studies within the same population as the MM-003 study. No randomised control trials (RCTs) were identified and the search was expanded to include non-RCTs. The company state it was not feasible to conduct a meta-analysis or mixed treatment comparison; therefore, the studies identified will not be discussed in detail¹⁵.

3.1 Study MM-003

3.1.1 Efficacy

This was a multicentre, open-label, randomised phase III trial conducted in adult patients diagnosed with refractory or relapsed and refractory multiple myeloma who had failed at least two treatment cycles of bortezomib and lenalidomide¹⁶. Patients (n = 455) either received pomalidomide 4 mg per day on days 1–21 and dexamethasone 40 mg per day on days 1, 8, 15 and 22 (POM+LoDex; n = 302); or dexamethasone 40 mg per day on days 1– 4, 9–12 and 17–20 (HiDex; n = 153). Both treatment regimens followed a 28-day cycle and the dexamethasone dose was reduced to 20 mg in all patients aged ≥ 75 years¹⁶. Patients were excluded if they had previously received pomalidomide, had resistance to HiDEX, peripheral neuropathy (≥ Grade 2), renal insufficiency (creatinine clearance < 45 ml/min) or if they were eligible for ASCT^{15,16}.

The primary end point was progression-free survival (PFS), based on the International Myeloma Working Group uniform response criteria (see Glossary)¹⁷. There were two pre-planned data cut-off dates, the first for final PFS and interim overall survival (OS) with a median follow-up of 4.2 months. At the first cut-off, the independent data monitoring committee (IDMC) recommended that people in the HiDEX group who had not progressed should have the option to receive pomalidomide (with or without dexamethasone)¹⁶. The second cut off date reported updated PFS and final OS, with a median follow-up of 10.0 months; a summary of these key results are presented in Table 1.

Table 1 Study MM-003 results for primary and secondary endpoints^{15,16}

Endpoint	POM+LoDEX (95% CI) n = 302	HiDEX (95% CI) n = 153	Analysis
Primary endpoint			
Median updated progression-free survival	4.0 months (3.6–4.7)	1.9 months (1.9–2.2)	HR 0.48 (0.39–0.60) p<0.0001
Secondary endpoints			
Final overall survival	12.7 months (10.4–15.5)	8.1 months (6.9–10.8)	HR 0.74 (0.56–0.97) p=0.0285
Time to progression	4.7 months (4.0–6.0)	2.1 months (1.9–2.5)	HR 0.46 (0.36–0.59) p<0.0001
Overall response rate	95/302 (31%)	15/153 (10%)	OR 4.22 (2.35–7.58)
Median response duration	7.0 months (5.8–9.0)	6.1 months (1.4–8.5)	HR 0.52 (3.25–1.05) p=0.0631
CI: confidence interval; HR: hazard ratio; OR: odds ratio. HiDEX: high dose dexamethasone; POM+LoDEX: pomalidomide plus low dose dexamethasone			

Results showed a statistically significantly longer PFS and OS in patients with advanced relapsed and refractory multiple myeloma treated with POM+LoDEX compared to HiDEX¹⁶. Other secondary endpoints and further subgroup analyses showed consistent results in favour of the POM+LoDEX regimen⁴. Health related quality of life (HRQL) questionnaires were completed by patients on day 1 of each treatment cycle and at treatment discontinuation¹⁵. Numerically, scores were better for the POM+LoDEX group compared to the HiDEX group for all domains at every cycle¹⁵.

3.1.2 Safety

In study MM-003 the safety population included all patients who had received at least one dose of study medicine (POM+LoDEX n = 300; HiDEX n = 150). A total of 247 patients in the POM+LoDEX group had treatment-emergent adverse events (TEAEs) considered to be associated with pomalidomide. The most common were neutropenia

(43%), anaemia (24.7%), fatigue (21%) and thrombocytopenia (19.3%)¹⁵. Serious adverse events (SAEs; grade 5, or requiring hospitalisation or resulting in disability or incapacity) were reported in 183 (61%) of the POM+LoDEX group and 80 (53%) of the HiDEX group¹⁶. In both treatment groups the most frequently occurring SAEs were pneumonia and general health deterioration⁴.

The most common adverse events (AEs) leading to discontinuation of pomalidomide were infections (pneumonia) and renal disorders (renal failure). Neutropenia, thrombocytopenia and pneumonia were the most common cause of dose reductions and interruptions of pomalidomide⁴. At the second data cut off point 146 (48.7%) patients in the POM+LoDEX group had died compared to 84 (56.0%) in the HiDEX group¹⁵. Progression of multiple myeloma accounted for 98 (68%) of deaths in the POM+LoDEX group and 51 (64%) in the HiDEX group¹⁶.

3.2 AW TTC critique

- At the time of licensing, the Committee for Medicinal Products for Human Use (CHMP) highlighted that the patient population under consideration has very limited treatment options⁴. Currently other options include palliation, a second ASCT, re-challenge with a previously effective treatment or enrolment in a clinical trial³. CHMP concluded that study MM-003 demonstrated POM+LoDEX to be superior to HiDEX with a clinically meaningful improvement in PFS and survival in multiple myeloma patients who have failed lenalidomide and bortezomib⁴.
- Retreatment with bortezomib plus dexamethasone was identified as the main comparator by the applicant company; however, no head to head comparison data were provided. The pivotal phase III study MM-003 used HiDEX as a comparator. The company state whilst there is no established standard of care for heavily pre-treated multiple myeloma patients, HiDEX was included in the MM-003 trial as a control arm after consultation with regulatory authorities, and because it has been widely used as an active comparator for testing other novel agents before their approval for relapsed or refractory multiple myeloma, including previous registration studies of lenalidomide and bortezomib¹⁸. However, the company claim that based on communication with clinicians in Wales, HiDEX is not standard care in Wales and is therefore not included as a comparator for the indication under consideration¹⁵. In addition to retreatment with bortezomib plus dexamethasone the company state other comparator options include off-label bendamustine used in combination with thalidomide and dexamethasone or with prednisolone¹⁵.
- Clinical expert opinion sought by AW TTC confirms treatment options are limited in Wales, and there is limited access to clinical trials for relapsed myeloma. It was also highlighted that bendamustine-based regimes are probably the most commonly used, although these are not routinely available in all areas of Wales.
- The applicant company conducted a systematic literature review to identify comparator studies. No RCTs were identified which enrolled a comparable cohort to patients enrolled in the POM+LoDEX group in study MM-003. Non-RCT studies were also considered to be similarly lacking in comparable patient population to the pivotal study¹⁵. The applicant company state an indirect comparison or a mixed treatment comparison was therefore not feasible as the evidence identified by literature review was from single arms of trials with no common comparator¹⁵.
- Pomalidomide is closely related to thalidomide and in view of the risk of teratogenicity, the SPC states that the conditions of the manufacturer's pregnancy prevention programme should be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential². CHMP concluded that the combination of POM+LoDEX appears to have a similar safety profile to other medicinal products of the same class with some differences, including a lower risk than thalidomide for neuropathy and a lower

risk than lenalidomide for thromboembolism. The safety profile of pomalidomide is considered acceptable, however to address issues related to safety CHMP stated that the applicant company should conduct a non-interventional post authorisation registry of patients treated with pomalidomide for relapsed and refractory multiple myeloma⁴.

- In study MM-003, nine patients in the HiDEX group crossed over to pomalidomide before disease progression and seventy five crossed over after disease progression; this may have affected the results in favour of the HiDEX group¹⁶.
- Pomalidomide is an oral preparation², whereas bortezomib is administered via the intravenous (IV) or subcutaneous route and bendamustine via the IV route^{19,20}, which may impact on patient preference and has the advantage that it does not require administration by a healthcare professional.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company has submitted a cost-utility analysis of pomalidomide in combination with dexamethasone compared to retreatment with bortezomib and dexamethasone. The patient population considered in the economic model are those with relapsed and refractory multiple myeloma who have been previously treated with at least bortezomib and lenalidomide, but also thalidomide, hence pomalidomide represents a fourth-line treatment option. UK/Welsh clinical experts consulted by the company indicated that in addition to re-treatment with agents used earlier in the treatment pathway, bendamustine is also used off-label in relapsed and refractory multiple myeloma patients. Hence, scenario analysis was conducted with bendamustine in combination with prednisolone, or in combination with thalidomide plus dexamethasone.

Patient level data from study MM-003 comparing POM+LoDEX with HiDEX was used in the economic model¹⁶. HiDEX was not considered by the company to be a relevant comparator due to lack of use in clinical practice in relapsed and refractory multiple myeloma, and an indirect comparison was stated not to be feasible due to the limited outcomes data for the appropriate comparators. Instead the HiDEX treatment arm data were used in the model as a proxy for the comparators of interest, based on the assumption that outcomes would be expected to be similar regardless of treatment received at this late stage of multiple myeloma. The company supported this assertion by reference to UK clinical advice they had received that little difference would be expected between active and palliative treatment at this line of therapy, and through regression analysis performed by the company showing no statistically significant effect of bortezomib or bendamustine treatment using data from a study of 30 relapsed and refractory multiple myeloma patients treated in a single UK centre²¹.

A Markov partitioned survival analysis model was developed with health states consisting of pre-progression (on treatment), pre-progression (off treatment), progressive disease and death. A model cycle length of 1 week was assumed with a 25-year time horizon. Extrapolation of time to treatment failure (TTF), PFS and OS was performed by fitting parametric functions to the observed data from study MM-003. There was significant patient cross-over to pomalidomide on disease progression in study MM-003 which confounds the OS results, hence a two-stage Weibull approach was utilised to address cross-over confounding in the economic model.

Costs included in the economic model covered medicine acquisition, medicine administration, funded transport, routine monitoring, adverse events management, terminal care, concomitant medication and use of blood transfusions. Acquisition costs for pomalidomide include a confidential discount on the current list price based on an

agreed Wales Patient Access Scheme (WPAS). Dosing and duration of POM+LoDEX treatment was estimated from the MM-003 study data, and based on SPC information for the comparators. [commercial in confidence information removed]. Utilities for the model health states (ranging between 0.65–0.75 for the pre-progression state, and between 0.57–0.71 for the post progression state, with utility dependent on response) were based on a regression analysis performed on EuroQoL five dimensions (EQ-5D) data from the MM-003 study. Grade 3/4 adverse event disutilities were based on published estimates or assigned zero disutility if assumed to be transitory or not associated with quality of life impact.

4.1.2 Results

The estimated incremental cost per quality-adjusted life year (QALY) gained for the base case comparison of pomalidomide plus dexamethasone versus bortezomib plus dexamethasone (as proxied by HiDEX outcomes) is [commercial in confidence figure removed], based on an incremental cost of [commercial in confidence figure removed] and incremental QALYs of 0.62 (Table 2). The main driver of the results is the additional medicine acquisition costs of pomalidomide. Bortezomib is estimated to result in higher administration costs due to IV administration, but lower monitoring costs than pomalidomide. Two thirds of the life years and QALY gains are estimated to be in the post-progression phase.

Table 2. Base case analysis results (incorporating WPAS for pomalidomide)

	POM+DEX	BOR+DEX	Increment	Plausibility
Medicine costs	¶¶¶	£14,815	¶¶¶	The lack of evidence on the efficacy of BOR re-treatment means the life years gained estimate and therefore the ICER is uncertain.
Other costs*	£14,195	£13,890	£305	
Total costs	¶¶¶	£28,705	¶¶¶	
Life years gained	2.22	1.15	1.07	
QALYs gained	1.27	0.65	0.62	
ICER (deterministic)			¶¶¶	
ICER (probabilistic)			¶¶¶	
ICER (probabilistic including weighted TTF, PFS and OS model averaging)[†]			¶¶¶	Illustrates impact of uncertainty in survival modelling

*These cover medicine administration, funded transport, monitoring/tests, blood transfusions, terminal care, subsequent therapy and concomitant medication and adverse event management costs. POM+DEX is estimated to have higher monitoring costs associated with regular monitoring for haematological toxicity during the first 8 weeks of treatment, but lower administration costs associated with oral administration for POM versus intravenous administration for BOR.

[†] This analysis included weighted TTF, PFS and OS model averaging (i.e. curves selected based on likelihood of each parametric function providing an optimal fit to the data using bootstrapping methods). Incremental costs estimated at [commercial in confidence figure removed] and incremental QALYs of 0.57.

¶¶¶Commercial in confidence data removed

BOR: bortezomib; DEX: dexamethasone; HiDEX: high-dose dexamethasone; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival; POM: pomalidomide; QALY: quality-adjusted life year; TTF: time to treatment failure.

In scenario analysis, incremental cost-effectiveness ratios (ICERs) of over [commercial in confidence figure removed]/QALY gained were estimated for the comparisons with regimens including bendamustine (Table 3).

Use of alternative estimates of comparator efficacy based on real world evidence from a retrospective study in 30 multiple myeloma patients receiving a range of therapies post bortezomib, lenalidomide and thalidomide treatment²¹ did not have a large impact on the base case ICER (Table 3). However, one-way sensitivity analysis demonstrated sensitivity to the uncertainty associated with OS function parameter estimates, and with variation in utility regression coefficients (Table 3).

The base case results were sensitive to the choice of parametric function for OS, with the use of an exponential function increasing the ICER to around [commercial in confidence figure removed] per QALY gained (Table 3). Probabilistic analysis generated a mean ICER estimate similar to the base case deterministic ICER, with a 15.7% probability of pomalidomide plus dexamethasone being cost-effective at a threshold of £30,000/QALY and 64.4% at a threshold of £50,000 per QALY gained. Including weighted TTF, PFS and OS model averaging in the probabilistic analysis resulted in a mean ICER estimate of [commercial in confidence figure removed] per QALY gained (Table 2), with a 51.6% probability of pomalidomide plus dexamethasone being cost-effective at a threshold of £50,000/QALY.

Table 3: Selected scenario and sensitivity analyses (incorporating WPAS for pomalidomide)

Scenario/sensitivity analysis	ICER (deterministic)	PSA results – probability POM+DEX cost-effective at £30,000/QALY	Plausibility
Base case	¶¶	15.7%	Uncertainty over the ICER due to lack of comparator survival data.
Scenario analyses			
Comparison with BEN+PRED	¶¶	1.9%	BEN for fourth-line multiple myeloma therapy is off-label use, but is one of a range of possible alternatives that are used. However, there is a lack of evidence for efficacy of BEN fourth line.
Comparison with BEN+THAL+DEX	¶¶	3.1%	
Comparator efficacy based on a real world (UK) study in relapsed/refractory multiple myeloma patients ²¹	¶¶	28.3%	Small study in only 30 patients hence survival estimates generated using this data are uncertain.
OS projection based on exponential function	¶¶	0.6%	There is some uncertainty over the most appropriate function based on model fit/visual fit. The log-normal comes out as the highest probability of being the most reliable model, but the exponential has a slightly higher probability than the base case log-logistic function.
OS projection based on log normal function	¶¶	25.5%	
Comparator OS estimated using RPSFTM for cross-over confounding	¶¶	17.8%	Uncertainty in survival and ICER associated with cross-over bias. However, RPSFTM is a recognised approach that provides a useful alternative assessment to the base case approach.
Bortezomib treatment duration restricted to 8 cycles as per SPC	¶¶	X	Base case model assumed bortezomib treatment until progression, in contrast to the SPC recommended maximum treatment duration of 8 cycles
One-way sensitivity analyses			
95% CI for OS log-logistic log (scale) parameter for POM+Dex	¶¶	-	The ranges illustrate the uncertainty in the ICER associated with uncertainty in the survival estimates for the comparator treatment, and sensitivity to utility regression estimates.
95% CI for EQ-5D utility regression intercept	¶¶	-	
¶¶Commercial in confidence data removed. BEN: bendamustine; CI: confidence interval; DEX: dexamethasone; EQ-5D: EuroQoL five dimensions; ICER: incremental cost-effectiveness ratio; OS: overall survival; PRED: prednisolone; PSA: Probabilistic sensitivity analysis; RPSFTM; Rank Preserving Structural Failure Time Modelling; THAL: thalidomide.			

4.1.3 AWTTTC critique

The company economic evaluation has used a standard partitioned survival economic model commonly used in the assessment of cost-effectiveness of cancer therapies. The base case ICER under the WPAS is [commercial in confidence figure removed] per QALY gained, the company has suggested that pomalidomide plus dexamthasone meets AWMSG specified end of life criteria in that relapsed and refractory patients receiving fourth-line treatment have a short current survival prognosis of 3–6 months, and the potential survival benefit associated with pomalidomide plus dexamthasone is

about 7 months versus HiDEX after cross-over adjustment. A key issue in the economic evaluation is the lack of comparative evidence versus therapies used in practice for the fourth-line treatment of multiple myeloma. An indirect comparison has not been performed but instead the comparisons with bortezomib retreatment, and bendamustine based regimens are based on assuming that any active treatment received at this late stage of multiple myeloma has comparable efficacy. This is the justification for using the HiDEX arm of the pomalidomide MM-003 trial as a proxy for the comparators considered. However, this means there is uncertainty over the survival and hence QALY benefit associated with the comparators.

The main strengths of the economic evaluation include:

- An appropriate model structure which was clearly specified.
- Extrapolation of survival benefits that used accepted methods for parametric function fitting, with appropriate sensitivity analysis. The application of weighted survival model averaging for TTF, PFS and OS is useful for addressing uncertainty in the selection of appropriate parametric functions based on statistical and visual best fit.
- Although a new approach has been used for addressing cross-over bias (the two-stage Weibull), the approach is supported by scenario analysis using a recognised approach, Rank Preserving Structural Failure Time Modelling (RPSFTM), which resulted in a slightly higher ICER of [commercial in confidence figure removed] per QALY gained.
- The health state utility regression analysis utilises the EQ-5D data from the pomalidomide trial and appears to be well performed, producing plausible PFS and progressive disease utility estimates.

Key limitations of the economic evidence are:

- There is uncertainty in the estimates of life years gained for POM+LoDEX related to selection of parametric function for OS, and the need to adjust for cross-over bias.
- The uncertainty in the outcomes associated with the comparator treatment is propagated by the lack of any direct evidence used in the model for bortezomib retreatment efficacy and survival outcomes in fourth-line multiple myeloma. The same limitation applies for the evidence for bendamustine regimens explored in scenario analysis. The use of the HiDEX arm of the MM-003 study as a proxy for bortezomib or bendamustine outcomes is highly uncertain. The evidence supporting the company assertion that the type of active therapy at fourth line does not impact on outcomes is limited. There remains the possibility that active treatments such as bortezomib retreatment may be more effective than HiDEX with more palliative intent in relapsed and refractory multiple myeloma treatment, especially in selected patients who have previously responded to bortezomib. If this is the case, the base case ICER will be underestimated. Moreover, the assumption of equivalence among comparator treatments suggests that benefits equal to those of bortezomib could be achieved with HiDEX for a much reduced cost. Additional analysis provided by the company demonstrated an ICER of [commercial in confidence figure removed] per QALY gained, which could be considered an upper estimate of the ICER for pomalidomide.
- The parametric curve fits for OS have some limitations in terms of visual fit to the MM-003 data, and OS estimates. At the tail of the observed data each of the parametric functions tested appear to be potentially overestimating POM+LoDEX survival, and underestimating OS for the comparator.
- Treatment practice at the fourth-line stage appears mixed with no defined standard of care. The company has provided ICER estimates for comparisons with bortezomib (base case) or bendamustine (scenario analysis) regimens, but not compared to HiDEX (the actual comparator in the MM-003 trial), or lenalidomide regimens. In addition, the real world evidence used by the

company shows that some patients at this treatment line receive no active therapy. Additional analysis provided by the company assuming a treatment mix based on a UK real world study²¹ which included 7% of patients receiving no treatment resulted in an ICER of [commercial in confidence figure removed] per QALY gained.

- The model has a time horizon of 25 years in the base case. This seems very long given the late stage of multiple myeloma represented by fourth-line treatment, and the budget impact model estimates 90% mortality by year 5 with pomalidomide treatment. Shortening the time horizon to 10 years in the model increases the deterministic ICER to [commercial in confidence figure removed] per QALY gained respectively.
- Pomalidomide treatment costs take account of non-protocol interruptions but it is not clear whether this has been taken into account for the comparators. In addition, bortezomib re-treatment costs in the base case analysis appear to be based on treatment until disease progression rather than the SPC recommended duration of 8 cycles, which leads to higher costs estimated for the comparator¹⁹. The company has provided a scenario analysis limiting bortezomib treatment to 8 cycles, in which the ICER increases to [commercial in confidence figure removed] per QALY; however, the company claims that longer duration of treatment than that specified in the SPC is in line with clinical practice, and published evidence from an observational study of bortezomib retreatment in multiple myeloma patients in a Swiss centre²².

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTTC have not identified any published evidence on the cost-effectiveness of pomalidomide within its current licensed indication for patients with relapsed and refractory multiple myeloma.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on commercial market research data, the company estimates there are 3,025 patients in the UK on third-line treatment with lenalidomide for multiple myeloma in the UK¹. Of these, 43% are estimated to continue onto fourth-line therapy based on analysis of lenalidomide trial data²³. A number of these patients are expected to enrol in ongoing and future trials and so have been omitted from the expected number of patients starting pomalidomide treatment. An estimate of 76.7% of patients who reach fourth-line therapy will be actively treated, based on data from the real world study in 30 relapsed and refractory UK patients treated in a single UK centre²¹. Applied to the population of Wales, the company estimates 37 multiple myeloma patients would be eligible for treatment with pomalidomide plus dexamethasone each year.

Based on reported current uptake in England from the Cancer Drugs Fund, the company estimates uptake in Wales to be 55% in year 1, rising to 75% in year 5. The base case estimate of numbers treated, taking account of mortality in the prevalent patient population across years 1–5, is presented in Table 4. The net budget impact is estimated based on annual per patient costs derived from the economic model.

5.1.2 Results

The base case net budget impact estimates are presented in Table 4.

The company also performed the same scenario analyses as conducted for the economic evaluation (section 4) to assess the impact on cumulative five-year budget impact estimates. Assuming displacement of bendamustine regimens rather than bortezomib had the largest impact, with a cumulative five-year budget impact of £4.1

million. In one-way sensitivity analysis varying the proportion of patients assumed to be receiving active fourth-line therapy had the greatest impact on the estimated budget impact, as would be expected. Probabilistic analysis produced a cumulative five-year budget impact estimate similar to the reported base case deterministic estimate.

Table 4. Company-reported base case budget impact of POM+ DEX in Wales (incorporating WPAS for pomalidomide)

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible and expected to receive active 4th line therapy patients[†]	37	56	66	73	78
Uptake in incident patient population (%)[*]	55%	60%	65%	70%	75%
POM+Dex Treated patients	20	32	41	48	55
Net costs based on displacement of BOR+DEX (base case)					
Net costs (Medicine costs)	£££	£££	£££	£££	£££
Administration and monitoring	£££	£££	£££	£££	£££
Primary care	£££	£££	£££	£££	£££
Secondary & tertiary care	£££	£££	£££	£££	£££
Staffing	N/A	N/A	N/A	N/A	N/A
Infrastructure	N/A	N/A	N/A	N/A	N/A
Personal social services	£££	£££	£££	£££	£££
Overall net cost	£££	£££	£££	£££	£££
Cumulative 5-year budget impact	£££				
[*] Uptake is as a proportion of incident cases which is estimated at 37 per year. [†] 76.7% of patients were assumed to be receiving active 4 th line therapy. Mortality with POM has been estimated at 49.8% in year 1 up to 90.1% by year 5, and 72.4% to 96.4% respectively without POM. £££Commercial in confidence data removed. BEN: bendamustine; BOR: bortezomib; DEX: dexamethasone; N/A: not available; POM: pomalidomide; PRED: prednisolone; THAL: thalidomide.					

5.1.3 AW TTC critique

- The company has adopted a pragmatic approach to estimate eligible patient numbers receiving 3rd line treatment for the UK and extrapolated this to Wales. However, the assumptions around the number of patients eligible for treatment based on expected trial enrolment would appear subject to a good deal of uncertainty.
- All uptake estimates relate to incident cases only; it is assumed no switching of prevalent cases would occur.
- The budget impact modelling is complex. The derivation of medicine and other, per patient, costs used in the budget impact assessment are unclear and the estimates reported in the submission differ from the figures included in the budget impact model.

5.2 Comparative unit costs

Acquisition costs for pomalidomide (Imnovid[®]) and potential fourth-line treatment options, based on current list prices, are shown in Table 5.

Table 5. Acquisition costs for medicines used in the treatment of relapsed and refractory multiple myeloma (fourth-line therapies)

Medicine	Doses*	Cost per cycle ^{† §}
Pomalidomide (Imnovid [®] ▼) and dexamethasone	For a 28-day cycle: POM: 4 mg once daily on days 1 to 21. DEX: 40 mg once daily on days 1, 8, 15 and 22.	£8,894
Bortezomib (Velcade [®]) and dexamethasone	BOR: 1.3 mg/m ² body surface area on days 1, 4, 8 and 11 of a 21-day cycle DEX: 40 mg once daily on days 1–4 and 8–11 for a 28-day cycle.	£3,070
Bendamustine (Levact [®]) [¶]	BEN: 120–150 mg/m ² body surface area on day 1 and 2 of a 28-day cycle.	£690–£830**
Thalidomide	THAL: 100–200 mg daily for a 28-day cycle	£597–£1,294
Lenalidomide (Revlimid [®]) and dexamethasone	LEN: 25 mg once daily on days 1–21 for a 28-day cycle. DEX: 1 st four cycles at 40 mg once daily on days 1–4, 9–12 and 17–20. Subsequent cycles at 40mg once daily on days 1–4.	1 st four cycles: £4,399 Subsequent cycles: £4,378
Dexamethasone	40 mg daily on days 1–4, 9–12 and 17–20 of a 28-day cycle.	£31
<p>*Doses based on SPCs^{1,16,17,24}</p> <p>[†]Costs are based on current BNF list prices as of March 2014²⁴</p> <p>[§]Dexamethasone has been calculated at a cost of £2.60 per day, which is an average cost based on the assumption of 50% use of 50 x 2 mg pack and 50% use of 100 x 2 mg pack.</p> <p>[¶]Bendamustine is licensed for first-line use in the treatment of multiple myeloma, hence is off label for fourth-line use. Cost range for 125 mg dose (1 x 100 mg vial, 1 x 25 mg vial) to 150 mg dose (1 x 100 mg vial, 2 x 25 mg vial)</p> <p>This table does not imply therapeutic equivalence of medicines or the stated doses. See relevant SPCs for full dosing details.</p>		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, pomalidomide (Imnovid[®]▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that pomalidomide (Imnovid[®]▼) will be supplied by a home healthcare provider¹⁵.

6.2 Ongoing studies

The company submission highlighted one ongoing study likely to be available within 6–12 months. Study CC-4047-MM-008 is a phase I, multicentre, open-label, dose-escalation study to determine the pharmacokinetics and safety of POM+LoDEX in patients with relapsed or refractory multiple myeloma and impaired renal function²⁵. Results are expected later in 2014 or early 2015¹⁵.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 07 November 2014

Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy on life-extending, end-of-life medicines

Consideration is required as to whether pomalidomide in the given patient population meets the end-of-life criteria set by the AWMSG Policy on appraising life-extending, end-of-life medicines^{9,27}.

The criteria for appraising life-extending, end-of-life medicines apply when the most plausible ICER estimate exceeds £30,000 per QALY gained, and all the following conditions are satisfied:

- The medicine is indicated for patients with a short life expectancy, normally less than 24 months (e.g. estimated from the median survival of patients in the control group of the pivotal study).
- There is sufficient evidence to indicate that the medicine offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment. The estimates of the extension to life (e.g. based on the difference in median survival in the pivotal trial, or projected life years gained) should be robust and shown (or reasonably inferred) from either PFS or OS.
- AWMSG/NMG will consider the cumulative population of each licensed indication of the medicine to be small.

The company suggest that pomalidomide in combination with dexamethasone should be considered under the AWMSG policy for appraising life-extending, end-of-life medicines, as the survival prognosis for patients with multiple myeloma who have progressed following treatment with bortezomib and lenalidomide is poor with a median survival of 3-6 months, the survival gain in the pivotal study versus HiDEX is 4.4 months, and the survival gain is increased to approximately 7 months when adjusted for crossover¹⁵.

The applicant company's base-case ICER for pomalidomide plus dexamethasone exceeds £30,000 per QALY when compared with bortezomib retreatment and dexamethasone. The company suggests that bortezomib retreatment and dexamethasone is the most relevant comparator; however, patient level data from study MM-003 comparing POM+LoDEX with HiDEX was used in the economic model. As HiDEX was not considered to be a relevant comparator and an indirect comparison was deemed infeasible, the HiDEX treatment arm data were used in the model as a proxy for the comparators of interest, based on the assumption that outcomes would be expected to be similar regardless of treatment received at this late stage of multiple myeloma¹⁵.

The OS of patients with refractory or relapsed and refractory multiple myeloma is poor. The company highlights a retrospective study in a single centre in the UK of 55 patients who had received, and become refractory to, thalidomide, bortezomib and lenalidomide sequentially. The study reported a median OS of 3.9 months after discontinuation of lenalidomide²⁸. In the pivotal study MM-003, the final OS in the control group (HiDEX group) was 8.1 months¹⁶.

The final OS in study MM-003 was 12.7 months in the POM+LoDEX group (HR 0.74 vs HiDEX, 95% 0.56 to 0.97, p=0.0285)¹⁶. The unadjusted, absolute difference in OS was

4.6 months and following adjustment for crossover effects the difference is approximately 6 to 7 months (depending on the method used).

NICE considers that $\leq 7,000$ patients in England would be considered to meet the definition of small under its end-of-life policy. Based on Office for National Statistics mid-2012 population estimates (53.5 million in England; 3.1 million in Wales)²⁹, thus a small cumulative population would equate to 406 patients in Wales. Pomalidomide is only licensed for use in the indication under consideration². The company considered only incident cases for its revised budget impact analysis, based largely on unpublished sources, but had previously obtained prevalence and mortality data for multiple myeloma in the UK from the NICE costing templates for a previous technology appraisal in multiple myeloma²². Incidence estimates were based on data from Cancer Research UK⁶. These data were adjusted for the population of Wales to produce an estimate of 384 prevalent cases and 199 incident annual cases of multiple myeloma in Wales. The proportion of patients previously treated with thalidomide, bortezomib and lenalidomide was estimated based on data from the NICE costing template for TA228²³, and the proportion actively treated was estimated from a real world study in 30 relapsed and refractory UK patients treated in a single UK centre²¹. This resulted in the number of eligible patients for the treatment of pomalidomide plus dexamethasone being estimated as 191 in year 1¹⁵.

GLOSSARY

International Myeloma Working Group (IMWG) uniform response criteria for progression-free survival (PFS)

Progressive disease requires one of the following:

- Increase of $\geq 25\%$ from nadir in:
 - Serum-M component (absolute increase ≥ 0.5 g/dl);
 - Urine-M component (absolute increase ≥ 200 mg/24 hours);
 - Bone marrow plasma cell percentage (absolute % $\geq 10\%$);
- Development of new or increase in the size of existing bone lesions or soft tissue plasmacytomas;
- Development of hypercalcaemia (corrected calcium > 11.5 mg/dl) attributed solely to plasma cell proliferative disease^{14,17}.

Relapsed myeloma

Previously treated patients who, after a period of being off-therapy require salvage therapy but do not meet the criteria for “relapsed and refractory” myeloma⁴.

Relapsed and refractory myeloma

Disease which has shown a minor response or better and then either become non-responsive whilst on salvage therapy or progressed within 60 days of the last therapy^{3,4}.

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