

Bortezomib for the treatment of multiple myeloma

Management of *relapsed* multiple myeloma

- Trend to manage later relapses more actively than previously
- Optimal therapy for relapsed myeloma not established. Includes:
 - thalidomide and lenalidomide (a derivative of thalidomide)
 - chemotherapy: alkylating agents (e.g. mephalan), anthracyclines
 - corticosteroids: dexamethasone, prednisolone
 - +/- stem cell transplant (auto/allo; BM/PB) with high dose therapy
 - combinations of the above
- Choice of treatment may depend on duration of first remission, prior therapies received and patients' clinical condition
- Ongoing research: NCRI/MRC Myeloma IX study
 - patients treatment naïve but protocol may indicate current UK practice
 - protocol being amended to include bortezomib plus dexamethasone at first relapse

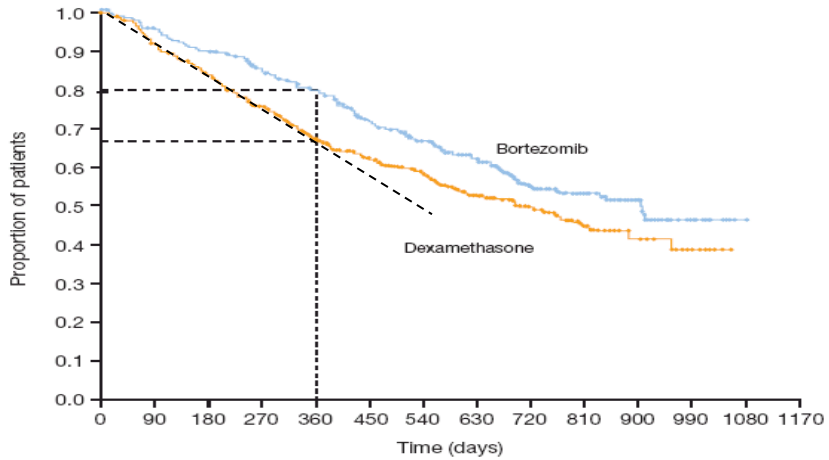
Bortezomib

- 1st new treatment licensed for use in relapsed MM for 10 years
- **Licensed indication:**
Bortezomib (Velcade, Janssen-Cilag) is indicated as *monotherapy* for the treatment of progressive multiple myeloma in patients who have received *at least one prior therapy* and who have *already undergone or are unsuitable for bone marrow transplantation*.
- 1st of a novel class of anticancer compounds: proteasome inhibitors
- Proteasomes are present in all cells
 - have role in regulation of key intracellular signalling proteins and normal cellular homeostasis
- Inhibiting protein degradation by the proteasome has the potential to:
 - drive cancer cells to apoptosis (programmed cell death)
 - prevent metastasis
 - overcome treatment resistance

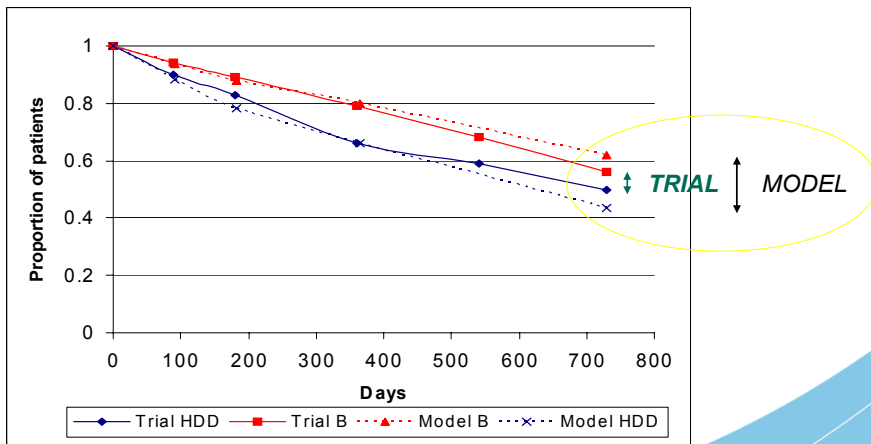
Bortezomib: costs

- £762.38 per 3.5mg vial
- Dose is 1.3mg/m² (1 vial assuming no sharing)
- 4 doses per 3-week cycle, so £3,049 per cycle
- Number of cycles varies but usually between 3 (£9,148) and 8 (£24,396) cycles
- Estimated mean drug cost in manufacturer's economic model (avg 25 doses): £19,060

Overall survival at 22 months follow up of APEX trial



Patient survival for HDD and bortezomib for the APEX trial and model results (p.42 ERG report)



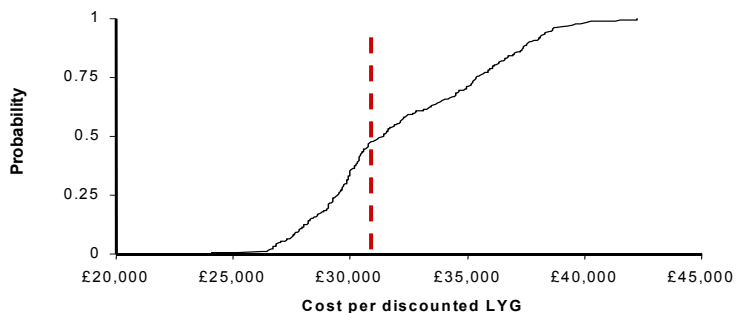
Cost effectiveness results : base case (1st relapse only)

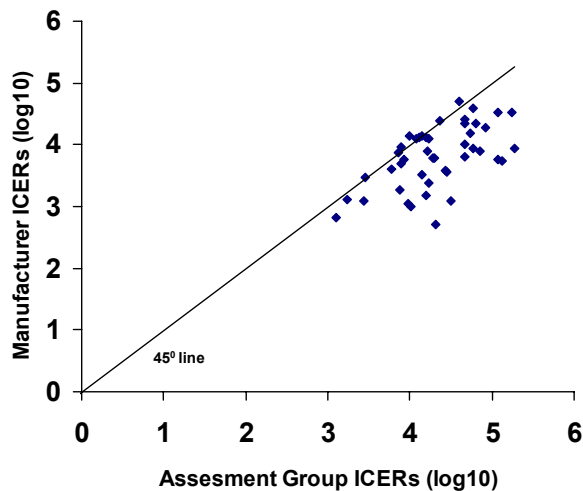
Outcomes	Bortezomib	HDD
Discounted survival (mths) (gain = 9.9)	32.6	22.7
QALYs (mths) (gain = 8)	26.3	18.3
Total treatment cost	£36K	£11K
Cost per LYG	£31K/LYG	-
Cost per QALY	£38K/QALY	-

Cost effectiveness: PSA (MS base case: 1st relapse only)

5th to 95th percentile: **£27K to 39K per LIFE YEAR GAINED**

Acceptability Curve





(Miners et al, BMJ 2005)

Appraisal Committee's preliminary recommendations

- 1.1 Bortezomib monotherapy, in its licensed indication, is not recommended for the treatment of patients with multiple myeloma except for use in well-designed clinical studies that focus on the establishment of the position of bortezomib in the pathway of care for people with multiple myeloma in comparison with other agents that are currently used in clinical practice in England and Wales.
- 1.2 People currently receiving bortezomib should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

Consultation on the ACD

- Consultee comments:
 - Manufacturer: 40 pages, including clarification of issues related to the APEX study and a revised economic report
 - Nominated clinical specialists and patient experts
 - Professional/Carer groups
 - DoH, WAG and DHSSPS Northern Ireland
- Web comments: > 300
- Letters from the public: > 90
- Other: letter from authors of APEX RCT
- Petition: > 3,000 signatures

British Committee for Standards in Haematology:

Position Statement on the use of bortezomib in multiple myeloma, 2005

- Referred to in many comments on the ACD
- “Clinical evidence would suggest benefits when **combined with dexamethasone** as a treatment for **second relapse**, as well as for patients at **first relapse who have been exposed to a range of therapies including thalidomide** as either induction therapy or as maintenance treatment.”
- UKMF: “it is estimated that 70% of patients with myeloma in the UK now receive a thalidomide containing regime as initial treatment.”

Revised results from Janssen-Cilag

Patient Group	Original Cost/QALY	Revised Cost/QALY	Revised 95% CI
1 st relapse	£38,052	£38,064	£33K to £47K
1 st relapse + stopping rule	£34,964	£33,515	£29K to £44K
1 st relapse + borte&dex	£35,410	£35,059	£34K to £48K
1 st relapse + borte&dex + stopping rule	£31,764	£30,586	£29K to £44K
1 st relapse + stopping rule + vial sharing	-	£30,112	£26K to £40K
1 st relapse + borte&dex + stopping rule + vial sharing	-	£27,566	£22K to £39K

Combination use: bortezomib + dexamethasone

Professional/patient/carer groups, clinical specialists, manufacturer:

- It is already common practice to use bortezomib in combination with intermediate doses of steroids which studies have shown to increase response rates at minimal additional cost.

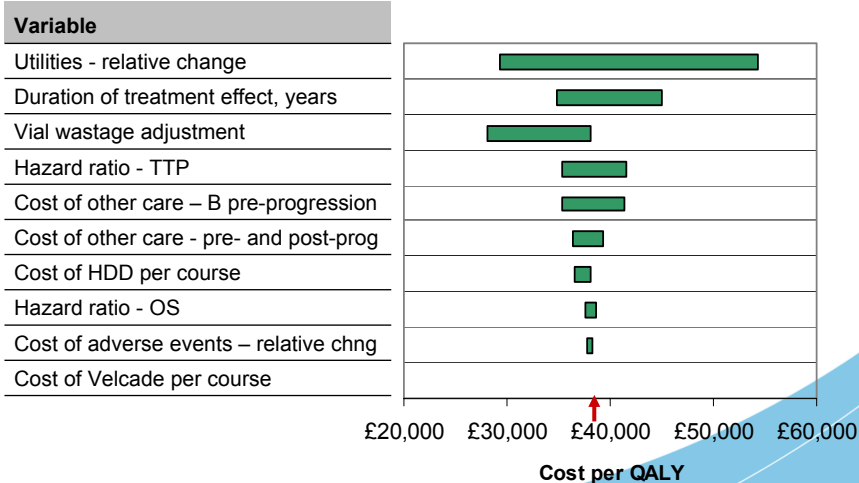
Manufacturer's submission:

- "Within the SmPC for Velcade, guidance is given with respect to the combination use with dexamethasone"

However the Marketing authorisation states:

- Section 4.1: bortezomib monotherapy is "indicated"
- Combination use with dexamethasone is only referred to in section 5.1, under sub-heading, 'clinical trials', which includes key results of the SUMMIT study (phase II)

One-way sensitivity analysis: First relapse (base case)



FAD – guidance

- 1.1 Bortezomib monotherapy is not recommended 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.
- 1.2 People currently receiving bortezomib monotherapy should have the option to continue therapy until they and their clinicians consider it appropriate to stop

Appeal Panel recommendations (1)

Appeal panel suggests that AC re-assess the evidence for the cost-effectiveness of bortezomib in the following circumstances:

1. use at first relapse
2. as in 1. including a 3-cycle stopping rule
3. as in 2. and when the manufacturer pays for treatment in patients who do not respond (not previously seen by AC)
4. combination therapy with dexamethasone (not to be discussed today)

Velcade Response Scheme (VRS)

- Rebate if not responding after up to 4 cycles (different from stopping rule in submission which was after 3 cycles)
- Rebate by replacement stock, or credit note (as easier to administer), cash rebate possible if requested
- Response evaluated by decrease in serum M-protein (different from APEX and previous submission which used EBMT, of which serum M-protein is a major part)
- Responder defined as having minimal response or better (different from submission which used partial or complete response)

Department of Health and Welsh Assembly Government (1)

- DoH has studied manufacturer's proposal in detail and discussed with the National Cancer Director and some of his clinical advisors.
- Believes scheme is reasonable in terms of its clinical basis
- Is satisfied that its proposed operation is transparent
- Believes that it will not impose a disproportionate organisational burden on relevant NHS organisations in England
- WAG fully agrees and endorses all points in DoH letter.

Bortezomib monotherapy for relapsed multiple myeloma

Guidance

- 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).
- 2 People currently receiving bortezomib monotherapy who do not meet the criteria in paragraph 1 should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

Implementation tools

NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TA129).

- Costing report and costing template to estimate the savings and costs associated with implementation.
- Audit criteria to monitor local practice.

Further information

Ordering information

You can download the following documents from www.nice.org.uk/TA129

- A quick reference guide (this document) – a summary of recommendations for healthcare professionals.
- 'Understanding NICE guidance' – information for patients and carers.
- The full guidance.
- Details of all the evidence that was looked at and other background information.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone the NHS Response Line on 0870 1555 455 and quote:

- N1354 (quick reference guide)
- N1355 ('Understanding NICE guidance').

Implementation

- Costing
- Administration rebate scheme
- Evidence active gathering
- Future comparisons

Drugs for the Treatment of Pulmonary Arterial Hypertension (PAH)

another difficult appraisal

Classification (WHO 2003)

- 1. Pulmonary arterial hypertension (PAH)
 - 1.1. Idiopathic (IPAH)
 - 1.2. Familial (FPAH)
 - 1.3. Associated with (APAH):
 - 1.3.1. Connective tissue disease (CTD)
 - 1.3.2. Congenital systemic to pulmonary shunts
 - 1.3.3. Portal hypertension
 - 1.3.4. HIV infection
 - 1.3.5. Drugs and toxins
 - 1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)
 - 1.4. Associated with significant venous or capillary involvement
 - 1.4.1. Pulmonary veno-occlusive disease (PVOD)
 - 1.4.2. Pulmonary capillary haemangiomatosis (PCH)
 - 1.5. Persistent pulmonary hypertension of the newborn (PPHN)

Licensed
indications

Functional Classes of PAH

- I Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnoea, fatigue, chest pain or pre-syncope.
- II Patients with pulmonary hypertension who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain or pre-syncope.
- III Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain or pre-syncope.
- IV Patients with pulmonary hypertension who are unable to perform any physical activity and who may have signs of right ventricular failure at rest. Dyspnoea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

Prognosis & prevalence

- 1980's average 2.8ys
 - 68% 1yr. Survival
 - 48% 3yr. Survival
 - 24% 5yr. Survival
- Worsening prognosis with increasing Functional class and reduced 6min walking test
- Poor recognition (symptomless) / 2000 Greater recognition: - demographics re proximity to centres
- IPAH 1-2 per million
- Other PAH 1-2 per million
- Likely prevalence 15-20per million
- Total estimate 2200pts

Technologies

- Prostaglandins (parenteral administration)
- Epoprostenol continuous IV infusion
 - synthetic prostacyclin (a vasodilating prostaglandin)
- Iloprost intermittent inhalation or IV (licensed for inhalation only)
 - synthetic stable prostacyclin analogue.
- Endothelin receptor antagonists (orally administered)
- Bosentan
 - endothelin is a potent vasoconstrictor which mediates its effect through receptors (ETA and ETB) Bosentan binds to both
- Sitaxentan
 - selective endothelin receptor antagonist (ETA)
- Phosphodiesterase V inhibitors (orally administered)
- Sildenafil
 - is a phosphodiesterase inhibitor
 - intracellular cyclic guanosine is a vasodilator broken down by phosphodiesterases

Results – clinical (AG)

- All five technologies added to supportive care and when used at licensed doses more clinically effective than supportive care alone
- Not possible to adequately compare technologies or combinations of technologies
- All lead to QALY improvement compared to supportive care
- Lack of long term data (in RCT) leads to questions about duration of treatment effects/ are these different with varying baseline entry FC?

RCTs concerns

- Rare disease with limited UK based studies
- All trials short duration (18/52 longest)
- Variety of PAH aetiologies investigated often outside licensed indications
- Variability of baseline FC
- Variability in measured/reported outcome measurements
- Trial design
 - Most RCT involved one technology plus supportive treatment with placebo and/or supportive treatment (ST)
 - 4 head to head comparisons of technologies (1 Epo v Bosentan+Epo; 1 Bosentan v Sitaxentan; 1 Bosentan v Silendafil; 1 Bosentan v Iloprost)

Comparators

- Scope: epoprostenol, iloprost, bosentan, sitaxentan, sildenafil will be compared with supportive treatments and with each other
- Manufacturers:
 - iloprost vs epoprostenol
 - bosentan vs epoprostenol
 - bosentan vs supportive treatment
 - sitaxentan vs supportive treatment
 - sitaxentan vs bosentan
 - sildenafil vs “background therapy”
- AG: each with supportive treatment vs supportive treatment

Cost Effectiveness results Manufacturers' submissions

- iloprost vs epoprostenol - iloprost dominant
- bosentan vs epoprostenol - bosentan dominant
- bosentan vs BSC - £84k (IPAH) and £78k (PAH/CTD)
- bosentan vs “historical care” - £21k (IPAH)/£15k (PAH/CTD)
- sitaxentan vs supportive treatment - £95k per LYG
- sitaxentan vs bosentan - £20k per LYG
- sildenafil - lifetime costs: SIL £123k BOS £186k ILO £224k EPO £305k SIX £184k

AG economic model

- Markov model, 30 year time horizon, EQ5D
- Population Venice category 1 (FCIII or IV)
- Intervention plus supportive treatment versus supportive treatment
- Costs, utilities, transitions centre on FC
 - Transition probabilities FC from RCTs
 - Survival/mortality on Rx from RCTs + background survival/mortality calculated via FC in RCTs
- Importance of avoidance of epoprostenol

Cost effectiveness results – Assessment Group

	FC IV	FC III (ICER (£/QALY))				
	Epo	Epo	Iloprost	Bosentan	Sitaxentan	Sildenafil
Original – Reference case	343,000	277,000	101,000	27,000	25,000	Dominates
Original – Alternative epoprostenol price	96,000	106,000	101,000	39,000	40,000	3,700

ICER summary

	FC IV	FC III (ICER (£/QALY))				
	Epo	Epo	Iloprost	Bosentan	Sitaxentan	Sildenafil
Original – Reference case	343,000	277,000	101,000	27,000	25,000	Dominates
Original – Alternative epo price	96,000	106,000	101,000	39,000	40,000	3,700
Additional analyses						
Q1: No Epo in FC IV		273,000	98,000	42,000	44,000	9,000

Budget impact – estimated annual

Drug name	Estimated number of patients	Estimated budget impact
Epoprostenol	20	£0.55 to £2.75m
Iloprost	100	£3.5 to £4.2m
Bosentan	1000*	£20.6m
Sitaxentan	1000*	£20.6m
Sildenafil	1000*	£5.1m

*An estimated 1000 patients would be eligible for oral therapies

Appraisal Consultation Document

- 1.1 Sildenafil is recommended, within its marketing authorisation, for the treatment of pulmonary arterial hypertension in adults.
- 1.2 Bosentan and sitaxentan, within their licensed indications, are recommended as treatment options for pulmonary arterial hypertension only for adults in whom:
 - sildenafil is contraindicated (see summary of product characteristics [SPC])
 - sildenafil, as prescribed in accordance with section 1.1, is not effective in controlling the person's symptoms or degree of pulmonary hypertension
 - sildenafil, as prescribed in accordance with section 1.1, is poorly tolerated.
- 1.3 Intravenous epoprostenol and inhaled iloprost are not recommended for the treatment of pulmonary arterial hypertension in adults
- 1.4 People who are currently receiving bosentan or sitaxentan (outside the recommendations in section 1.2), intravenous epoprostenol or inhaled iloprost should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

Implementation

- National Specialised Commissioning
- Cooperative Regional Specialised Commissioning
 - Yes to epoprostenol in FCIV
 - Yes to sildenafil first
- NICE adding value?
 - Ultra-orphan
 - National guidance available
 - 'Small' budget impact