

**NHS England**

**Evidence review: Bendamustine for Relapsed  
Multiple Myeloma**



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First published: May 2018

Updated: Not applicable

Prepared by: Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

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## 1 Introduction

### Introduction

- Multiple myeloma, also known as myeloma, is a type of bone marrow cancer. Multiple myeloma affects the plasma cells inside the bone marrow. Myeloma does not usually take the form of a lump or tumour. Instead, the myeloma cells divide and expand within the bone marrow, damaging the bones and affecting the production of healthy blood cells. Myeloma often affects many places in the body. Commonly affected areas include the spine, skull, pelvis and ribs (NHS Choices 2018).
- In the early stages, myeloma may not cause any symptoms. It is often only suspected or diagnosed after a routine blood or urine test. However, myeloma will eventually cause a wide range of problems, including a persistent dull ache or specific areas of tenderness in bones, weak bones that break/fracture easily, tiredness, weakness, shortness of breath (caused by anaemia) and repeated infections. Less commonly it causes bruising and unusual bleeding such as frequent nosebleeds, bleeding gums and heavy periods (NHS Choices 2018). Approximately 70% of patients have bone pain on diagnosis and 30% have high calcium blood levels (hypercalcaemia) causing excessive thirst and urine production. In later stages of the disease patients may develop renal failure and swollen ankles (NHS England 2018).
- There is one main type of myeloma. The cells produce large quantities of an abnormal antibody (immunoglobulin), known as a paraprotein. This has no useful function and lacks the ability to fight infection. In each case of myeloma only one type of immunoglobulin (Ig) is overproduced and IgG is the most common. IgM, IgD and IgE are very rare. All these types of myeloma are treated in the same way. About 20% of people produce an abnormal immunoglobulin (light chain myeloma) and rarely, approximately 3%, produce no immunoglobulin at all (non secretory myeloma) (NHS England 2018).

### Existing guidance from the National Institute of Health and Care Excellence (NICE)

- NICE guidelines for first line therapy for multiple myeloma include the use of bortezomib, thalidomide, steroids and stem cell transplantation (NICE guidelines 2016).
- For relapsed or progressive multiple myeloma NICE recommends the use of bortezomib, lenalidomide and further stem cell transplantation (NICE guidelines 2016).
- Bendamustine is currently listed by the Cancer Drugs Fund for the treatment of relapsed multiple myeloma where all of the following conditions are met: application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy; relapsed disease where all other treatments contraindicated or inappropriate; used within the treating Trust's governance framework, as Bendamustine is not licensed in this indication (NHS England Cancer Drugs Fund 2018).

### The indication and epidemiology

- Multiple myeloma is an uncommon type of cancer, with 5540 new cases diagnosed in 2015 in the UK. Myeloma accounted for 2% of all cases of cancer in 2015 in the UK. Myeloma incidence rates have increased by 32% since the 1990s (National Cancer Intelligence Network 2018).
- It is not known exactly what causes the condition, although it is more common in people with Monoclonal Gammopathy of Unknown Significance (MGUS) – an excess number of protein molecules called immunoglobulins in the blood, and is more common in men and adults over 60. Most cases are diagnosed at around the age of 70 and cases affecting

people under the age of 40 are rare (NHS Choices 2018).

- Myeloma is an incurable disease. The main aims of treatment are to prolong survival and maintain quality of life. Patients without symptoms, known as smouldering or indolent myeloma, do not normally require treatment. For patients needing treatment, interventions are guided by symptoms and the results of investigations. Treatment is usually with a combination of chemotherapy, biological therapies and steroids. There are multiple options approved by NICE and these are usually given until either disease progression or intolerable toxicity has occurred. Eventually, the patient may have exhausted all NICE-approved therapies but may still be fit for further active treatment (NHS England 2018).

### **Standard treatment and pathway of care**

- The initial treatment for multiple myeloma may be either non-intensive for older or less fit patients or intensive – for younger or fitter patients. Both non-intensive and intensive treatments involve taking a combination of anti-myeloma medicines. Intensive treatment involves much higher doses and is followed by a stem cell transplant (NHS choices 2018).
- Further treatment is needed if myeloma returns. Treatment for relapses is generally similar to initial treatment, although non-intensive treatment is often preferred to further intensive treatment. Additional medications such as lenalidomide, pomalidomide, and other chemotherapy medicines such as carfilzomib and ixazomib may be added as appropriate (NICE 2016).

### **The intervention (and licensed indication)**

- Bendamustine is an active bifunctional alkylating agent. It is currently licensed for the first line treatment of myeloma in patients over 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy precluding the use of thalidomide or bortezomib (NHS England 2018).
- This review is to consider evidence for the use of bendamustine in the treatment of patients with relapsed multiple myeloma who are chemotherapy-refractory or chemotherapy-intolerant. Bendamustine is not licensed for this indication.

### **Rationale for use**

- The rationale for using bendamustine in people with relapsed chemotherapy-refractory or chemotherapy-intolerant multiple myeloma is that it has two ways of working (as an alkylating agent and as a purine analogue) and has only partial cross resistance with other alkylating agents, so people not responding to or not able to tolerate other alkylating agents or other chemotherapy agents may respond to it (Leoni et al 2008 and NHS England 2018).

## **2 Summary of results**

- The evidence review found four uncontrolled studies. These included a total of 272 patients who had relapsing multiple myeloma that had been heavily pre-treated. All four studies were retrospective using information retrieved from case notes. The proportion who were treated with concomitant steroids ranged from 38% to 100%. Outcomes reported include overall survival, progression free and event free survival, response rates and toxicity.
- **Overall survival (OS):** Four uncontrolled studies reported median overall survival between 5.5 months and 17 months. The lowest of these (Kim et al 2016) (n=65, OS 5.5 months, 95%

confidence interval (CI) 3.5 to 7.5) showed the majority of patients experiencing early progression or treatment related adverse events. Damaj et al (2012) showed a median OS of 12.4 months (n=110, no CI provided). Stohr et al (2015) showed a median OS of 17 months (n=58, CI not provided), as did Michael et al (2010) (n=39).

- **Progression free survival (PFS) / Event free survival (EFS):** Kim et al (2016) showed a median PFS of 3.1 months (95% CI 2.4 to 3.8), the majority of patients showing early progression. In the Damaj et al (2012) study the median PFS was 9.3 months and 66% of patients who responded to bendamustine remained in response for more than six months. Michael et al (2010) showed a median 7 months EFS, as did Stohr et al (2015) (CIs not provided).
- **Overall response rate (ORR):** All four studies described ORR. The proportion of patients showing a response to bendamustine varied from 30% (Damaj et al 2012) to 59% (Stohr et al 2015). The proportion showing a complete response varied from 0% (Stohr et al 2015 and Michael et al 2010) to 2% (Damaj et al 2012 and Kim et al 2016), and the proportion showing a partial response varied from 20% (Stohr et al 2015) to 36% (Michael et al 2010).
- **Safety:** The extent of reporting of adverse events varied in these uncontrolled studies. Three studies reported toxicity related adverse events. Most frequently reported adverse effects were haematological. Severe (grade 3/4) anaemia was experienced by between 10% (Michael et al 2010) and 71% (Stohr et al 2015). Severe neutropenia/leucopenia was experienced by between 16% (Stohr et al 2015) and 65% (Kim et al 2016), and severe thrombocytopenia was experienced by between 21% (Stohr et al 2015) and 46% (Kim et al 2016). Fifteen percent experienced severe infection in the Michael et al study (2010). There were five deaths from sepsis and five deaths from pneumonia in the Kim et al study (2016) (n=65).
- **Subgroup analysis:** Where a comparison was made between outcomes using bendamustine doses above and below 120mg/m<sup>2</sup>, no significant differences were found. The only significant difference found when comparing the use of concomitant steroids with treatment with bendamustine alone, was a higher rate of infections in patients who received steroids (33% vs 0%, p=0.04, n=39) (Michael et al 2010).
- Regarding potentially prognostic subgroups, although not surprisingly some associations were found between relevant prognostic variables and OS or EFS, without a comparator group that did not receive bendamustine, it is not possible to assess whether there were any subgroup differences relating to the effectiveness or safety of bendamustine treatment.
- Overall, the evidence base is limited to uncontrolled, retrospective studies, which are at risk of selection bias and which do not allow a comparison of outcomes with outcomes for patients treated with best supportive care without bendamustine. The limitations of the evidence base limit the strength of conclusions that can be drawn.
- Thus although there is some weak evidence that bendamustine might help to slow progression for a short period of time in some patients, the types of studies found mean that it is not possible to have any level of confidence about either the effectiveness or the toxicity of bendamustine in this group of patients.
- **Cost effectiveness:** No studies assessing the cost effectiveness of bendamustine with or without steroids for patients with refractory or relapsed multiple myeloma were identified.

### 3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).

- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: e.g. EMBASE and MEDLINE and the Cochrane Library (see section 10 for search strategy).
- The search dates for publications were between 9th March 2008 and 8th March 2018.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful, were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO, were selected for inclusion in this review. Because no studies were found that matched the PICO, it was agreed with NHS England that studies without a comparator group (case series), which matched the population and intervention criteria stated in the PICO, would be included in this review.
- Studies were excluded if they were already included in literature reviews.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

## 4 Results

A total of four papers matching the population and intervention defined in the PICO were included; all were uncontrolled retrospective studies: Kim et al (2016)(n=65); Stohr et al (2015)(n=58); Damaj et al (2012)(n=110); Michael et al (2010)(n=39).

The studies ranged in size from 39 to 110 participants, and included a total of 272 participants. Only one study (Damaj et al 2012) explicitly stated the median follow up period, which was 10 months. Full details of the study designs and outcomes are summarised in the evidence tables in section 7.

### **Question 1. What is the evidence on clinical effectiveness of using bendamustine +/- steroid compared with best supportive care for individuals with relapsed multiple myeloma who are chemotherapy-refractory or chemotherapy-intolerant?**

The outcomes reported in the studies included overall survival, progression free survival, event free survival and overall response for patients with multiple myeloma who received bendamustine +/- steroid after prior treatments with other lines of chemotherapy and/or autologous stem cell transplantation (ASCT). Further details of the outcomes reported are provided in the tables in sections 7 and 8.

#### **Overall survival (OS)**

Overall survival was reported by four studies.

The Kim et al (2016) study found a median OS of 5.5 months (n=65, 95% CI 3.5 to 7.5). Median dose was 120mg/m<sup>2</sup>. The median number of bendamustine cycles patients had was two (range 1 to 5). All patients had concomitant steroids with bendamustine. The OS for those who responded

to bendamustine was significantly better than for those who did not respond ( $p=0.036$ ).

The Stohr et al (2015) study found a median OS of 17 months ( $n=58$ , CI not provided). Mean dose of bendamustine was  $120\text{mg}/\text{m}^2$  (range 60 to  $300\text{ mg}/\text{m}^2$ ). The median number of bendamustine cycles patients had was three (range 1 to 8). Thirty-eight percent had concomitant steroids with bendamustine. No significant difference was observed in OS relating to monotherapy versus bendamustine treatment combined with steroid ( $p=0.85$ ) or relating to dose of bendamustine above or below  $120\text{mg}/\text{m}^2$  ( $p=0.58$ ).

The Michael et al (2010) study found a median OS of 17 months ( $n=39$ , CI not provided). Mean dose of bendamustine was  $100\text{mg}/\text{m}^2$  (range 80 to  $150\text{ mg}/\text{m}^2$ ). The median number of bendamustine cycles patients had was three (range 1 to 10). Sixty-nine percent had concomitant steroids with bendamustine.

The Damaj et al (2012) study found a median OS of 12.4 months ( $n=110$ , CI not provided). Dose of bendamustine varied from 60 to  $150\text{ mg}/\text{m}^2$ . The median number of bendamustine cycles patients had was four (range 1 to 13). All patients had concomitant steroids with bendamustine.

### **Event free survival (EFS) / Progression free survival (PFS)**

Although using different terms, the four studies define EFS and PFS as time from first bendamustine treatment to disease progression or death (Stohr et al 2015 and Damaj et al 2012) or as time from first bendamustine treatment to disease progression, relapse or death (Kim et al 2016 and Michael et al 2010).

Michael et al (2010) showed a median EFS of 7 months ( $n=39$ , CI not provided). The Stohr et al (2015) study also showed a median EFS of 7 months ( $n=58$ , CI not provided). Median PFS was reported by Kim et al (2016) as 3.1 months (95% CI 2.4 to 3.8), and by Damaj et al (2012) as 9.3 months ( $n=110$ , CI not provided). Damaj et al (2012) also reported that 66% of patients who responded to bendamustine, remained in response for more than six months from the beginning of bendamustine treatment (22 of 33 patients), although follow-up was not long enough to measure the median duration of response.

Stohr et al (2015) found no difference in EFS between those receiving bendamustine alone compared to those treated with bendamustine plus steroid (EFS 7 months for both groups,  $p=0.6$ ).

### **Overall response (ORR)**

Kim et al (2016) defined the ORR as the proportion of patients who had a complete response (CR), a very good partial response (VGPR) or a partial response (PR) to treatment (defined as the best response achieved, even if patients' disease went on to progress before the end of treatment), and observed an ORR of 35% (23 of 65 patients). CR was observed in one patient (2%), VGPR in five (8%) and PR in 17 (26%). Eighteen patients (28%) showed early disease progression during treatment (PD). The number with stable disease (SD) was not reported.

In the Stohr et al (2015) study, there were adequate data to evaluate 44 patients regarding response rate. The ORR was defined as the proportion of patients who had a CR, PR or minimal response (MR), and was 59% (26 of 44 patients). There was no complete response (CR) observed. Twenty per cent ( $n=9$ ) had a PR and 39% ( $n=17$ ) achieved a MR. Comparing those who had bendamustine with and without concomitant steroid, response rates were 59% in both groups. There was also no significant difference relating to the dose of bendamustine above or below  $120\text{mg}/\text{m}^2$  (53% vs 64%,  $p=1$ ).



Damaj et al (2012) defined ORR as the proportion of patients who had a CR or PR to treatment, and observed an ORR of 30%, with CR in two patients (2%) and PR in 31 (28%). SD was observed in 22 patients (20%) and PD in 55 patients (50%).

In the Michael et al study (2010), the ORR, defined as CR plus PR, was 36% (14 of 39 patients), with a VGPR in one patient and a PR in 13. CR was not observed. Seven patients (18%) had a MR to treatment, with SD in ten patients (26%) and PD in eight (20%). 33% (n=13) of patients stopped treatment due to remission.

**Question 2. What is the evidence relating to the safety of bendamustine +/- steroid compared with best supportive care for individuals with relapsed multiple myeloma who are chemotherapy-refractory or chemotherapy-intolerant?**

Adverse events were reported in three uncontrolled retrospective studies - all except the Damaj et al (2012) study. The reporting of adverse events varied. Most frequently reported adverse effects were haematological side effects. Toxicity was graded by the Common Terminology Criteria for Adverse Events (CTCAE), where grade 1=mild, grade 2=moderate, grade 3=severe, grade 4=life threatening.

In the study by Kim et al (2016) five of 65 patients died of sepsis and five due to pneumonia. Three died of sepsis after the first treatment with bendamustine, and of the remaining 62 patients, grade 3/4 neutropenia was observed in 65% (n=39), grade 3/4 anaemia was observed in 22% (n=14) and grade 3/4 thrombocytopenia in 46% (n=30). Ten patients discontinued treatment due to infectious complications. Other adverse events were less severe (grades 1/2) and less frequent, and included four further cases of pneumonia and one of sepsis, as well as fatigue (n=10), sensory neuropathy (n=6) and anorexia (n=2).

Stohr et al (2015) observed grades 3/4 anaemia in 71% of 58 patients (n=41), grade 3/4 leucopenia in 16% (n=9), and grade 3/4 thrombocytopenia in 21% of patients (n=12). Non-haematological reactions were mild, including a mild allergic reaction in two patients. No grade 3/4 non-haematological adverse effects were observed. No relationship was seen between grade of anaemia and either bendamustine dose or whether steroids were used concomitantly or not (p values not provided). Note that of the 30 patients with grade 4 anaemia, only six developed it during or after bendamustine treatment (24 had had this prior to commencing bendamustine therapy).

Michael et al (2010) observed grades 3/4 anaemia in 10% of 39 patients (n=4), grades 3/4 thrombocytopenia in 26% (n=10), grades 3/4 neutropenia in 41% (n=16) and grades 3/4 infection in 15% (n=6). Infections were significantly more frequent in those who were treated with concomitant steroids (33% vs 0%, p=0.04). One patient had a paravertebral abscess with spondylodiscitis requiring surgical treatment. Other non-haematological side effects were all grades 1/2 and included fatigue (n=2), nausea and vomiting (n=3), diarrhoea (n=2), urticaria (n=1), paraesthesia (n=1) and an increase in creatinine (n=3). Ninety five percent of side effects occurred after the first cycle of bendamustine treatment. This study found no significant difference in haematological toxicity between dose levels of bendamustine, whether or not steroids were used, whether the patient had had prior high dose therapy or ASCT, or by age (p values not provided).

**Question 3. What is the evidence on the cost effectiveness of bendamustine +/- steroid compared with best supportive care for individuals with relapsed multiple myeloma who are chemotherapy-refractory or chemotherapy-intolerant?**

No studies were identified which assessed the cost effectiveness of bendamustine +/- steroid for patients with relapsed multiple myeloma who are chemotherapy-refractory or chemotherapy-intolerant.

**Question 4. Does the evidence of clinical and cost-effectiveness identify any subgroups of patients with relapsed multiple myeloma who are chemotherapy-refractory or chemotherapy-intolerant who would gain greater benefit from using bendamustine +/- steroid compared with best supportive care?**

Because there was no comparator group that did not receive bendamustine treatment in any of the studies, it is not clear whether any subset of patients benefited from bendamustine treatment. Some of the uncontrolled studies evaluated outcomes for different patient groups treated with bendamustine. These are described below. However the differences do not necessarily indicate different amounts of benefit from bendamustine treatment in different groups of patients because the groups may also have had different outcomes without bendamustine treatment.

**Overall survival (OS):**

Kim et al (2016) reported higher OS in patients with a higher Eastern Cooperative Oncology Group (ECOG)<sup>1</sup> performance status (ECOG 0/1 vs ECOG>1) (p=0.025). A trend towards improved OS was observed in patients less than 60 years old (p=0.059, not significant), whereas the median number of prior lines of treatment prior to bendamustine treatment (<5 vs ≥5) was not associated with OS (p=0.951).

In the Stohr et al study (2015) no significant difference in median OS was observed for patients with IgG subtype (21.8 months) compared to the IgA subtype (13.1 months) (p=0.18). Nor was there a significant association with the number of prior lines of therapy (≤3 or >3) (p=0.83). Using Cox regression analysis, Stohr et al (2015) also found no significant association between OS and a number of other relevant prognostic factors. Nevertheless, they then carried out hazard ratio (HR) analysis for OS and found the following HRs: severe thrombocytopenia HR=1.8; severe anaemia HR=1.4; primary refractory disease HR=1.4; prior ASCT HR=1.5; calcium level HR 15; and Salmon and Durie<sup>2</sup> stages II and IIIa disease compared to stage IIIb HR=0.4. However, p values and CIs were not provided and Cox regression analysis did not find any of these differences to be statistically significant. HRs for creatinine level, lactate dehydrogenase (LDH) level, age and sex ranged from 0.9 to 1.1 (no p-values or CIs provided).

Michael et al (2010) found a lower OS in patients with: stages II and III compared to stage I disease (p=0.001); elevated LDH (greater than 200 U/l) (p=0.02); and elevated CRP level >0.6mg/dl (p=0.001).

**EFS / PFS:**

Although the presentation of the results is not clear it appears that Stohr et al (2015) found a significant association using Cox regression analysis between EFS and calcium level (p=0.02) and prior ASCT (p=0.03), but no significant association with a number of other relevant prognostic factors tested. Nevertheless, they then carried out HR analysis for EFS and found the following HRs: severe anaemia HR=1.6; primary refractory disease HR=2.4; prior ASCT HR=3.9, calcium level HR 16 and Salmon and Durie stages II and IIa compared to stage IIIb HR 0.5. For other factors tested, HRs were closer to 1. However, no p values or CIs were provided. Damaj et al (2012) found no significant difference in EFS in patients over or under 65 years of age, nor in

<sup>1</sup> ECOG is Eastern Cooperative Oncology Group System, used to assess how the disease affects the daily living abilities of the patient, and can help assess how a patient's disease is progressing and appropriate treatment and prognosis.

<sup>2</sup> Salmon and Durie staging system gauges the clinical stage of disease - stage I, II, or III a and IIIb, I being least advanced, IIIb being most advanced)

those who had had previous high dose therapy or ASCT (p values not provided). Michael et al (2010) suggested that metaphase cytogenetics is a predictor of EFS (p=0.05) but found no difference relating to age over and under 65.

**ORR:**

Stohr et al (2015) found no significant association between ORR and whether patients received  $\leq 3$  or  $>3$  prior lines of therapy (p=0.218), nor between patients with IgG compared to IgA subtypes of multiple myeloma (p=0.08).

No strong evidence was found to identify any specific subgroups who would gain greater benefit from the use of bendamustine +/- steroid compared to best supportive care. The lack of evidence comparing the intervention with a comparator prevents this comparison being made.

## 5 Discussion

The primary outcome of interest is whether patients who are heavily pre-treated and have chemotherapy-resistant or chemotherapy-intolerant relapsed multiple myeloma will benefit from having bendamustine plus or minus a steroid as a salvage therapy. The four studies included a total of 272 patients and found median OS rates ranging from 5.5 to 17 months, EFS or PFS rates ranging from 3.1 to 9.3 months and ORRs ranging from 30% to 59%, although definitions used for the latter varied between the studies. Relatively high rates of severe (grade 3 and 4) anaemia (10% to 71%), severe leucopenia/neutropenia (16% to 65%) and severe thrombocytopenia (21% to 46%) were also observed in these studies, and in one study five patients died of sepsis and five died of pneumonia (Kim et al 2016, n=65).

However, the evidence review only found uncontrolled studies that were retrospective. No comparative studies, whereby a comparable group of patients were given best supportive care, were found. Therefore it is not possible to tell how the outcomes for patients with chemotherapy-refractory or chemotherapy-intolerant multiple myeloma treated with bendamustine compare to outcomes for a comparable group of patients treated with standard best current supportive care without bendamustine. For example, it appears that a proportion of patients had a few months of progression free survival (median 3.1 to 9.3 months in these four studies). However, without a comparator we cannot be sure that this would not have occurred without bendamustine treatment. Similarly for the other outcome measures such as overall survival, we do not know whether the survival seen in these studies was longer than it may have been without bendamustine. It is not clear whether evidence from higher quality studies is likely to be published in future.

It is important to note that overall response to treatment reported by the studies did not necessarily mean that there was a sustained or substantial response. For example, Kim et al (2016) reported that the overall response rate (ORR) was based on the best response achieved and patients were counted as having responded even if they responded and then went on to progress before the end of treatment. In all of the studies, the definitions for response were not clearly defined, and some, such as Stohr et al (2015), included patients who had a minimal response.

Except for Damaj et al (2012), the case series included in this review did not explicitly state that the patients included were all resistant or intolerant to other types of chemotherapy, only that they were heavily pre-treated and that bendamustine was used as a salvage therapy. There may therefore have been other drugs which may have been a better choice for some of the patients, and the populations of these studies may not completely reflect the PICO for this review. Also, the populations in these studies were not always clearly restricted to populations that had

experienced the same previous combinations of treatments and interventions, and treatment pathways in Korea, France and Germany may differ from those in the UK, reducing the generalisability of some of the results.

Additionally, the retrospective nature of the data gathering in all of the included studies introduces a potential for bias. This is because of potential subjectivity in decisions regarding patients included in the analysis and the classification of patients and outcome information from records. For example, in Kim et al (2016), data were from patients treated at ten haematological institutions in Korea and information was retrieved by investigators from participating institutions. It is not clear whether these investigators were independent of the clinical teams.

The four uncontrolled studies varied in size from 39 to 110 participants. Two were based in Germany, one in France and one in Korea. The Korean Study assessed treatment outcomes where patients may have withdrawn from treatment due to lack of ability to fund treatment, potentially introducing bias. The other three studies did not report that patients stopped treatment for any financial reasons.

For the three out of the four studies where toxicity was measured, the side effects were judged by the study authors to be 'mild'. However, on analysis, the proportion and therefore numbers of patients experiencing severe and life threatening adverse events following bendamustine salvage therapy was generally relatively large. These were particularly haematological side effects such as anaemia, thrombocytopenia and leucopenia and infections such as pneumonia and sepsis. However, without a control group of patients, it is not clear how often these were caused by the bendamustine and/or steroid treatment, as opposed to being symptoms of the multiple myeloma. Baseline data provided was not sufficient to allow a comparison with levels of, for example anaemia, prior to treatment with bendamustine.

The decision regarding whether or not to use concomitant steroids in the two studies in which steroids were only used in a proportion of patients (Stohr et al 2015 and Michael et al 2010), was taken by the treating physician, and criteria for steroid use were not described and may have varied between clinicians. It is not clear how much the steroid may have contributed to any effect or toxicity seen, because the groups that did and did not receive concomitant steroids may not have been comparable.

Stohr et al (2015) could not find significant differences in OS or EFS in relation to a number of relevant potential prognostic variables such as age, creatinine and anaemia using Cox regression analysis, but nevertheless went on to calculate and report hazard ratios for these factors without reporting any associated p values or CIs. This is not usual or good practice, as only the most appropriate statistical test should be carried out. Additionally, the table presenting the results of both analyses was not clearly labelled.

Finally, none of the studies included a measure of quality of life.

## 6 Conclusion

The evidence identified for using bendamustine +/- steroid compared with best supportive care for individuals with relapsed multiple myeloma that are chemotherapy-refractory or chemotherapy-intolerant included four uncontrolled retrospective studies. With no controlled studies available, it is not clear whether bendamustine made a difference in the control of the symptoms or progression of heavily pre-treated multiple myeloma. For example, it appears that a proportion of

patients had a few months of progression free survival. However, we cannot be sure, without a comparator group, whether this might have also occurred without bendamustine treatment.

The severe toxicity experienced by patients should be considered alongside the paucity of evidence for increased survival time or slowing of disease progression. However, it is also not clear how many of the symptoms were related to toxic effects of bendamustine or to the multiple myeloma itself.

Thus although there is some weak evidence that bendamustine might help to slow progression for a short period of time in some patients, the types of studies found mean that it is not possible to have any level of confidence about either the effectiveness or the toxicity of bendamustine in this group of patients.

## 7 Evidence Summary Table

For abbreviations see list after each table

Use of Bendamustine plus or minus prednisone for relapsed multiple myeloma (no comparator)									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Kim et al 2016	S2  Uncontrolled retrospective multicentre case series  10 institutions in Korea  Patients treated in 2011-2013  Response rates and toxicities analysed in April 2014  Final survival status update in Dec	Patients with multiple myeloma who were refractory to last treatment or disease progressing following partial response  Median of 5 (range 2-12) previous treatments prior to first bendamustine treatment.  Median time from diagnosis to bendamustine treatment 3.8 years.  Median age 63 years. (range 38-77 years)	n= 65  Bendamustine 120mg/m <sup>2</sup> days 1 and 2 with Prednisone 60mg/m <sup>2</sup> per day or fixed dose of 100mg days 1-4  28-day treatment cycles.  Median number of treatment cycles 2 (range 1-5)  No control group	Primary  Clinical effectiveness	Overall survival (OS)	At endpoint 59 patients had died. 6 survived.  Median OS after bendamustine 5.5 months (95% confidence interval (CI) 3.5-7.5)  OS in those who responded to bendamustine was significantly better than that of those who did not respond to the drug (p=0.036)  OS in those with a higher Eastern Cooperative Oncology Group <sup>4</sup> (ECOG) performance status was significantly better than those with a lower performance status (ECOG 0/1 vs ECOG>1) (p=0.025)  Median number of treatment lines prior to bendamustine was not associated with OS (p=0.951).	6	Direct	As the study does not include a comparator it is not possible to compare the outcomes for patients treated with bendamustine with patients receiving alternative treatments.  Patients were heavily pre-treated, the majority (80%) refractory to their last treatment, while the remaining 20% relapsed following some response. However, the study population may include some patients who did not have chemotherapy-resistant or chemotherapy-intolerant disease, and thus may not completely match the population described in the PICO.  Retrospective design introduces possible selection bias in the study population, resulting from potential subjectivity in decisions regarding patients included in analysis and the classification of patients from records. In this study the data was from patients treated at 10 haematological institutions in Korea and information was retrieved by investigators from participating institutions, which means that selection may have been less objective than if information was retrieved by independent researchers.  The overall response rate (ORR) was based on the best response achieved, categorised as either complete response (CR), very good partial response (VGPR) or partial response (PR), and patients were counted as having responded even if they responded and then went on to progress before the end of treatment.

<sup>4</sup> ECOG is Eastern Cooperative Oncology Group System, used to assess how the disease affects the daily living abilities of the patient, and can help assess how a patient's disease is progressing and appropriate treatment and prognosis.

**Use of Bendamustine plus or minus prednisone for relapsed multiple myeloma (no comparator)**

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
	2015 Medical record reviews and data collections performed by investigators from participating institutes	Male to female ratio 1.5:1  Responses to last previous treatment were refractory disease (n=52, 80%) or disease progression from partial response (n=13, 20%)  55% (36) patients had previous autologous stem cell transplant (ASCT)  International Staging System (ISS) <sup>3</sup> at diagnosis stage I=7 Stage II=20 Stage III=35		Secondary  Clinical effectiveness	Progression free survival (PFS) Defined as survival duration from treatment start to relapse or progression or death.	Median PFS 3.1 months (95% CI 2.4-3.8)			39 patients stopped treatment due to a lack of response, 10 due to infection complications and 16 patients stopped for other reasons including costs because for some patients a lack of national insurance coverage for bendamustine prevented continuous treatment, even if they had responded to it. It is not known how many patients this applied to or how it may have affected the results.  No robust measure of quality of life was included so the impact of the side effects and toxicity of the treatment on the patients' quality of life is not known.
				Primary  Clinical effectiveness	Overall response rate=complete response (CR) +very good partial response (VGPR) + partial response (ORR)	Response calculated in 62/65 patients; 3 died after first treatment. (not evaluated)  CR=1, VGPR=5, PR=17 ORR=35% (23/65)  18 showed disease progression (PD) during treatment			
				Primary  Safety	Toxicities  Common Terminology Criteria for Adverse Events, (CTCAE) Version 3.0,  Grade 1 Mild AE, Grade 2 Moderate AE, Grade 3 Severe AE, Grade 4 Life-	5 patients died due to complications of sepsis (3 of whom died after the first treatment cycle), 5 died due to complications of pneumonia. A further 4 patients had grades 1/2 pneumonia and 1 had grade 1/2 sepsis. 10 patients discontinued treatment due to infectious complications.			

<sup>3</sup> The International Staging System (ISS). looks at the results of 2 blood tests. These blood tests are  $\beta$ 2-microglobulin and albumin. This system is used to predict response to treatment. These stages indicate different levels of projected survival rates and are staged at Stage I, Stage II and Stage III.

**Use of Bendamustine plus or minus prednisone for relapsed multiple myeloma (no comparator)**

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
					threatening or disabling AE  Grade 5 Death related to AE.	Grade 3/4 neutropenia occurred in 65% (39); Grade 3/4 anaemia in 22% (14); Grade 3/4 thrombocytopenia in 46% (30); Most non-haematologic toxicities (eg sensory neuropathy (6), nausea, diarrhoea, anorexia (2), fatigue (10)) were less severe than grade 3 and were less frequent			
Stohr et al 2015	S2  Uncontrolled retrospective analysis, multicentre case series  2 centres in Germany  2001 to 2011.	Diagnosis of relapsed or refractory multiple myeloma,  Aged over 18 years  Median age=69 (range 43-85)  Male n=23 Female n=35  No prior bendamustine treatment.  Median of 4 (range 1-10)	n=58  Bendamustine on day 1 and day 2 of 28-day cycle.  Median dosage 120mg/m <sup>2</sup> (range 60-300mg/m <sup>2</sup> )  38% (n=22) received steroid at median dose 40mg on day 1-4 and day 9-12  Median of 3 cycles of treatment (range 1-8)	Primary  Clinical effectiveness	Overall survival (OS)	Kaplan-Meier procedure and curves used to characterise survival function.  Median OS=17 months  Hazard ratio showed strength of associations between prognostic factors and OS.  Monotherapy vs treatment plus steroids, median OS 17 vs 13.5 months (p=0.85)  Dosage less than 120mg/m <sup>2</sup> OS=16.7 months v dosage 120-300mg/m <sup>2</sup> OS=15 months (p=0.58)  Median OS for IgG subtype 21.8 months v	8	Direct	This uncontrolled retrospective review included 58 patients from 2 centres.  Patients were heavily pre-treated, the majority refractory to their last treatment. All patients had been heavily pre-treated with at least 4 previous courses of therapy including vincristine, adriamycin, melphalan, cyclophosphamide, lenalidomide and bortezomib. Not all patients had been exposed to immune modulating agents or proteasome inhibitors, which might be important regarding response rate. Thus the study population may include some patients who were not resistant or intolerant to chemotherapy, and thus may not completely match the population described in the PICO.  Retrospective design introduces possible selection bias in the study population, resulting from potential subjectivity in decisions regarding patients included in analysis and the classification of patients from records. In this study the data were from patients treated at the University hospital Bonn and Klinikum Chemnitz, both Germany, and we have no information about who retrieved the data. Thus selection is likely to be less objective than case



**Use of Bendamustine plus or minus prednisone for relapsed multiple myeloma (no comparator)**

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		<p>previous types of therapy.</p> <p>Median time from diagnosis to 1<sup>st</sup> bendamustine treatment 3.5 years (range 0.1-12)</p> <p>Salmon and Durie stages<sup>5</sup>: IIa n=1, IIIa n=40, IIIb n=14 Missing n=3</p> <p>n=20 (34%) had previous ASCT, 10 of these received ASCT twice.</p>	No control group.			<p>13.1 months for IgA subtype (p=0.18)</p> <p>Number of prior lines of therapy, OS was 16.8 months for less than 3 and 14 months for more than 3 prior lines of therapy. (p=0.83)</p> <p>Cox regression analysis found no statistically significant association between reduced OS and relevant prognostic factors. Despite this, hazard ratios (HRs) were calculated: severe thrombocytopenia HR=1.8; severe anaemia HR=1.4; primary refractory disease HR=1.4; prior ASCT HR=1.5; Salmon and Durie stages IIa and IIIa compared to stage IIIb HR=0.4. For creatinine level, LDH level, age and sex HRs all between 0.9 and 1.1. No p-values or CIs provided for any of the HRs.</p>			<p>inclusion in a clinical trial.</p> <p>No comparator group of patients was included so it is not clear how the outcomes for patients who received bendamustine compares with outcomes for comparable patients not treated with bendamustine, and hence we do not know how effective bendamustine is compared to best supportive care or other treatments.</p> <p>The decision regarding whether or not to use concomitant steroids was taken by the treating physician and criteria for their use were not described and may have varied between clinicians. It is not clear how much the steroid may have contributed to any effect or toxicity seen, because the groups that did and did not receive concomitant steroids may not have been comparable.</p> <p>Having found no significant associations with Cox regression, the study went on to calculate hazard ratios, which is not usual/good statistical practice. No p values or CIs were presented in relation to the hazard ratios and the table presenting the results of both analyses was not clearly labelled.</p> <p>No robust measure of quality of life was included so the impact of the side effects and toxicity of the treatment on the patients' quality of life is not known.</p> <p>The duration of follow up was not stated.</p>
				Primary	Event free survival (EFS)	Kaplan-Meier procedure and curves			

<sup>5</sup> Salmon and Durie staging system gauges the clinical stage of disease (stage I, II, or III a and IIIb) by assessing levels of M protein, the number of lytic bone lesions, haemoglobin values, serum calcium levels and renal function.

**Use of Bendamustine plus or minus prednisone for relapsed multiple myeloma (no comparator)**

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
				Clinical effectiveness	Defined as time from 1 <sup>st</sup> day of treatment to death or disease progression	<p>used to characterise survival function.</p> <p>Median EFS=7 months</p> <p>Monotherapy vs treatment plus steroids: EFS both 7 months (p=0.6)</p> <p>Cox regression analysis suggested associations between EFS and calcium level (p=0.02) and prior ASCT (p=0.03) but no significant associations with other prognostic factors.</p> <p>Despite this, HRs were calculated: severe anaemia HR=1.6; primary refractory disease HR=2.4; prior ASCT HR=3.9; calcium level HR=16. Other HRs were closer to 1. No p values or CIs provided for any HRs.</p>			
				Secondary Clinical effectiveness	ORR ORR= CR + PR + minimal response (MR)	<p>Data were available to evaluate 44 patients for response rates.</p> <p>The ORR during treatment was 59% (n=26):</p> <p>CR 0%</p> <p>PR 20% (n=9)</p>			

Use of Bendamustine plus or minus prednisone for relapsed multiple myeloma (no comparator)

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
						<p>MR 39% (n=17)</p> <p>SD 27% (n=12)</p> <p>PD 14% (n=6).</p> <p>Comparing those who had bendamustine alone (n=27) and those who had bendamustine plus steroid (n=17), response rates were both 59% (p=1)</p> <p>ORR for those who received more (n=23) or less (n=21) than 120mg/m<sup>2</sup> of bendamustine was 53% v 64% (p=1)</p> <p>Regarding Ig subtype response rates were 57% for patients with IgG disease (n=30) and 64% with IgA disease (n=14) (p=0.08)</p> <p>Patients receiving 3 or less prior lines of therapy (n=20) had ORR 65%, while for &gt;3 prior lines of therapy (n=24) ORR 54% (p=0.218)</p>			
				Secondary Safety	Toxicities Common Terminology Crite	Anaemia observed in 79% (n=46) of patients. Grade 4 anaemia in 53% (n=30), of whom			

**Use of Bendamustine plus or minus prednisone for relapsed multiple myeloma (no comparator)**

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
					<p>ria for Adverse Events, (CTCAE) Version 3.0,</p> <p>Grade 1 Mild AE, Grade 2 Moderate AE, Grade 3 Severe AE, Grade 4 Life-threatening or disabling AE</p> <p>Grade 5 Death related to AE.</p>	<p>24 already had grade 4 anaemia prior to bendamustine treatment; and Grade 3 anaemia in 19% (n=11).</p> <p>There was no significant difference (no p-value given) regarding anaemia between monotherapy and concomitant steroid treatment.</p> <p>No association between bendamustine dose and grade of anaemia (no p-value given)</p> <p>Leucopenia observed in 60% (n=35) of patients; 2 (3%) had Grade 4 leucopenia and 7 (12%) had Grade 3 leucopenia.</p> <p>Thrombocytopenia observed in 40% (n=23): This was Grade 3 in 8 (14%) and Grade 4 in 4 patients (7%). No association seen between dosage or concomitant steroid use and grade of thrombocytopenia (no p-value given)</p> <p>2 patients suffered mild</p>			

**Use of Bendamustine plus or minus prednisone for relapsed multiple myeloma (no comparator)**

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
						<p>allergy to bendamustine- generalised exanthema and mild bronchospasm. Reactions not dose related.</p> <p>Other adverse events included mild fatigue, nausea, and vomiting.</p> <p>1 patient experienced worsening neuropathic pain.</p> <p>No grade 3/4 non-haematological side effects were documented.</p>			
Damaj et al, 2012	S2 Uncontrolled retrospective multicentre case series 13 centres in France 2007-2009	Patients with refractory or relapsing multiple myeloma after prior therapies which included alkylators, steroids, immunomodulatory imide drugs (IMiDs) and bortezomib.  Median age 63 (range 34-83)	n=110  Bendamustine dose 60-150 mg/m <sup>2</sup> day 1 and 2 every 28 days  Per protocol steroid was prednisone, the dose varied, no range given  Median no of cycles 4 (range 1-13)  35% (38) patients	Primary  Clinical effectiveness	ORR (defined as CR+PR)	<p>Median follow up of 10 months, 61 patients remained alive at end of study, 1 lost to follow up</p> <p>n=110 ORR=30% (n=33) CR =2% (n=2) PR =28% (n=31) SD =20% (n=22) PD =50% (n=55)</p> <p>Median PFS=9.3 months</p> <p>No significant difference in outcome with dose of bendamustine 80-100mg/m<sup>2</sup>, PR 33%</p>	6	Direct	<p>This uncontrolled retrospective review included 110 patients from 13 centres and had a relatively large sample size.</p> <p>It was stated that patients in this study had chemo-resistant or intolerant disease and had already been exposed to all available effective drugs. Patients were heavily pre-treated, the majority refractory to their last treatment.</p> <p>Retrospective design introduces possible selection bias in the study population, resulting from potential subjectivity in decisions regarding patients included in analysis and the classification of patients from records. In this study the data was from patients treated at 13 centres in France which provided complete medical records for all consecutive patients receiving at least one dose of bendamustine.</p> <p>No comparator was included so cannot compare outcomes for these patients with those receiving</p>

**Use of Bendamustine plus or minus prednisone for relapsed multiple myeloma (no comparator)**

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		<p>Male =67, female=43</p> <p>ISS at diagnosis Stage I=27 Stage II=30 Stage III=18</p> <p>90 cases had clear evaluation of disease before bendamustine, 71 of these patients progressing on last treatment,</p> <p>Median time from diagnosis to bendamustine treatment 60 months (range 10-224)</p> <p>Previous ASCT=66</p>	<p>received less than 3 cycles, 28% (31) received more than 6 cycles.</p> <p>Median follow-up 10 months.</p> <p>No control group</p>			<p>versus 120-150mg/m<sup>2</sup> PR 38% (p=0.8)</p> <p>No significant difference in outcome between bendamustine as monotherapy PR=25%, versus concurrent use of steroids PR=40% (p=0.48)</p> <p>No significant difference in PFS for patients older than 65 or under 65, (no p-values given)</p> <p>No significant difference in outcome with previous high dose therapy or ASCT (no p-values given)</p> <p>For patients who responded to treatment, 66% remained in response more than 6 months after start of bendamustine therapy (median duration not reached by end of study for this group).</p>			<p>alternative care.</p> <p>No measures were included relating to quality of life and hence no conclusion can be drawn regarding the effect of bendamustine on quality of life compared with best supportive care</p> <p>Evaluation of toxicity data was not one of the objectives of this trial and retrospective data on side effects were not collected.</p>

**Use of Bendamustine plus or minus prednisone for relapsed multiple myeloma (no comparator)**

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
				Primary Clinical effectiveness	OS	Median OS=12.4 months			
Michael et al (2010)	S2 Uncontrolled retrospective case series  Dusseldorf, Germany  2000-2005	Patients with refractory or relapsing multiple myeloma, with no previous bendamustine treatment.  Dosage of bendamustine greater than 80mg/m <sup>2</sup>  Complete data about 1 <sup>st</sup> line treatment, remission rate and EFS.  Median of 2 lines of prior treatment. Range (1-5)  64% had	n=39  Median dose 100mg/m <sup>2</sup> (range 80-150 mg/m <sup>2</sup> ) on day 1 and 2.  Concomitant steroids, physician decision. 31% (n=12) received bendamustine monotherapy, 69% received concomitant steroid.  Retrospectively allocated to 2 different groups, 80-100mg/m <sup>2</sup> (n=20) or 120-150 mg/m <sup>2</sup> (n=19)  Cycle repeated	Primary Clinical effectiveness	EFS (defined as time from first bendamustine treatment to disease progression, relapse or death)	Kaplan-Meier curves used with log rank test.  Median EFS 7 months.  Univariate analysis showed metaphase cytogenetics as a predictor for EFS (p=0.05)	Direct	8	In this study 54% of patients were refractory to their last salvage therapy and 46% suffered from progressive disease after a remission or stable phase.  The duration of follow-up was not stated.  Retrospective design introduces possible selection bias in the study population, resulting from potential subjectivity in decisions regarding patients included in analysis and the classification of patients from records. In this study the data was from patients treated at Heinrich Heine University, Dusseldorf, Germany. We have no information about who retrieved the data. This selection is likely to be less objective than case inclusion in a clinical trial.  No comparator was included so cannot compare outcomes for these patients with those receiving alternative care.  The decision regarding whether or not to use concomitant steroids was taken by the treating physician and criteria for their use were not described and may have varied between clinicians. It is not clear how much the steroid may have contributed to any effect or toxicity seen, because the groups that did and did not receive concomitant steroids may not have been comparable.  No robust measure of quality of life was included so
				Primary Clinical effectiveness	OS	n=39  Kaplan-Meier curves used with log rank test.  Median OS=17 months.  Patients with ISS stage II or III vs stage I, elevated LDH (greater than 200 U/l) , or elevated CRP level >0.6mg/dl had significantly shorter OS (p=0.001, p=0.02 and p=0.001 respectively)			
				Primary	ORR=CR+PR	ORR=36% (n=14)			

**Use of Bendamustine plus or minus prednisone for relapsed multiple myeloma (no comparator)**

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		<p>previous high dose therapy and ASCT</p> <p>23% had previous 2nd high dose therapy as salvage.</p> <p>59% had previous thalidomide.</p> <p>54% refractory to last salvage therapy.</p> <p>28% had extra medullary manifestations.</p> <p>Average age 61 years (range 41-81), 38% male, 62% female</p>	<p>median 28 days (range 14-90)</p> <p>Median of 3 cycles (range 1-10)</p>	Clinical effectiveness		<p>CR=0 VGPR=3% (n=1) PR=33% (n=13) MR=18% (n=7) SD=26% (n=10) PD=20% (n=8)</p> <p>In 33% (n=13) patients treatment stopped after PR, median 3 cycles (range 1-9) due to ongoing remission.</p> <p>No significant difference in outcome with dose of bendamustine 80-100mg/m<sup>2</sup> PR 33% (n=7) vs 120-150mg/m<sup>2</sup> PR 38% (n=7) (p=0.8)</p> <p>No significant difference in outcome between bendamustine as monotherapy PR=25% (n=3), compared to concurrent use of steroids PR=40% (n=11) (p=0.5)</p> <p>No difference between remission outcomes for patients older or under 65 (no p-value given)</p>			the impact of the side effects and toxicity of the treatment on the patients' quality of life is not known.
				Safety Toxicity	Toxicities were graded according to CTCAE (Common	Toxicity mild to moderate, mainly haematological adverse events.			



**Use of Bendamustine plus or minus prednisone for relapsed multiple myeloma (no comparator)**

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
					<p>Terminology Criteria For Adverse Events) Version 3.0 and max toxicity grade recorded.</p>	<p>95% of side effects occurred after administration of 1st cycle of bendamustine.</p> <p>Severe anaemia (grade 3 or 4) in 10% (n=4) of patients required red blood cell transfusion.</p> <p>41% (16) grade 3-4 neutropenia, 15% (6) required IV antibiotics. 1 paravertebral abscess with spondylodiscitis required surgical intervention</p> <p>Other toxicity mainly gastrointestinal, grade 1-2 nausea and vomiting 8% (3) and grade 1/2 diarrhoea 5% (2).</p> <p>Other grade 1-2 toxicities were fatigue (n=2), increased creatinine (n=3) paraesthesia (n=1), urticaria (n=1). No grade 3/4 non-haematological toxicities observed.</p> <p>No statistically significant difference in haematological toxicity between dose levels of</p>			

**Use of Bendamustine plus or minus prednisone for relapsed multiple myeloma (no comparator)**

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
						<p>bendamustine or between those receiving concomitant steroids or monotherapy (p value not given)</p> <p>Infection statistically significantly more frequent in patients receiving steroids 33% vs. 0% (p=0.04)</p> <p>No difference in toxicity by age or by those receiving prior high dose therapy with ASCT (p-values not given)</p>			

Abbreviations: ASCT - Autologous stem cell transplant; CR – complete response; CTCAE - Common Terminology Criteria for Adverse Events; ISS - International Staging System; LDH - lactate dehydrogenase; ORR - overall response rate; MR-minimal response; PD - progressive disease; PR – partial response; SD - stable disease; VGPR – very good partial response

## 8 Grade of Evidence Table

For abbreviations see list after each table

Use of Bendamustine plus or minus steroid for relapsed or refractory multiple myeloma (no comparator)					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Overall survival (OS)	Kim et al (20106)	6	Direct	A	<p>Overall survival (OS) is the length of time from first bendamustine treatment to the time of death. In these studies it was reported as the median overall survival for the group of patients, which is the number of months after first treatment with bendamustine that 50% of the patients survived.</p> <p>Stohr et al (2015) was the best quality study for this outcome measure, being larger and more recent than Michael et al (2010). Stohr et al (2015) found a median OS of 17 months (n=58). No evidence was found for an association between the dose of bendamustine used (above or below 120mg/m<sup>2</sup>) and median OS (15 vs 16.7 months) (p=0.58). There was also no significant difference observed in median OS when bendamustine was used alone (OS 17 months) compared to its use in conjunction with steroids (OS 13.5 months) (p=0.85).</p> <p>This result suggests than on average patients with relapsed or refractory multiple myeloma survived 17 months following commencement of bendamustine therapy.</p> <p>Because the study had no comparator group of patients receiving best supportive care without bendamustine, we do not know whether bendamustine is more or less effective in terms of OS than best supportive care. Additionally the study had a relatively small sample size and was retrospective, with the possibility of bias in relation to which patients were and were not included.</p>
	Stohr et al (2015)	8	Direct		
	Damaj et al (2012)	6	Direct		
	Michael et al ((2010)	8	Direct		
Progression Free	Kim et al (20106)	6	Direct	B	Progression free survival (PFS) and

**Use of Bendamustine plus or minus steroid for relapsed or refractory multiple myeloma (no comparator)**

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Survival (PFS) / Event free survival (EFS)					<p>event free survival (EFS) were both defined in these studies as the time from first bendamustine treatment to disease progression or death or (for two of the studies) relapse.</p> <p>Stohr et al (2015) was the best quality study for this outcome measure, being larger and more recent than Michael et al (2010). Stohr et al (2015) found median EFS to be 7 months (n=58), and found no difference in EFS when bendamustine was used alone compared to its use in combination with steroids (EFS 7 months for both, p=0.6). Although reporting was unclear, Cox regression analysis suggested an association between EFS and calcium level (p=0.02, hazard ratio (HR) 16) and prior ASCT (p=0.03, HR 3.9).</p> <p>This suggests that on average patients with relapsed or refractory multiple myeloma survive for 7 months following first bendamustine treatment before progression of disease, relapse or death, and that factors such as calcium level and prior treatment may affect survival.</p> <p>The implications of the results of the study are not entirely clear as there is no comparison made with patients who did not have the bendamustine treatment, and we do not know how long the latter group might survive without measurable disease progression. This is an uncontrolled retrospective study. The design of the study, i.e. looking back at case notes, introduces the possibility of selection bias in the selection of patients for the study and in the study population outcome information obtained, as it is possible that not all the relevant patients or information are included in the study</p>
	Stohr et al (2015)	8	Direct		
	Damaj et al (2012)	6	Direct		
	Michael et al ((2010)	8	Direct		
Overall Response	Kim et al (2016)	6	Direct	A	The ORR is defined as the proportion of

**Use of Bendamustine plus or minus steroid for relapsed or refractory multiple myeloma (no comparator)**

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
rate (ORR)					<p>patients whose multiple myeloma tumour size/markers respond to the bendamustine treatment, whether partially or completely.</p> <p>Stohr et al (2015) found an ORR of 59% among 58 patients with relapsed or refractory multiple myeloma, of whom 44 could be evaluated for response. No complete remission was observed. 20% (9 patients) had a partial response and a further 39% (17 patients) had a minimal response. No significant difference was found in ORR when groups who received bendamustine with and without a steroid were compared (59% in both groups), nor when a dose of bendamustine above and below 120mg/m<sup>2</sup> were compared (53% vs 64%) (p=1).</p> <p>This suggests that 59% of patients had some response to bendamustine treatment. However the response may have been small and short-lived.</p> <p>This is an uncontrolled retrospective study of a relatively small sample size (n=58). The lack of comparator in the study limits the strength of conclusions that can be drawn. Additionally, the impact, if any, of a minimal response on patients' quality of life or overall survival is not known. The retrospective design of the study introduces the possibility of bias in the selection of patients for the study and in the outcome information obtained, as it is possible that not all the relevant patients or information were included.</p>
	Stohr et al (2015)	8	Direct		
	Damaj et al (2012)	6	Direct		
	Michael et al (2010)	8	Direct		
Safety - toxicity	Kim et al (2016)	6	direct	A	<p>Toxicity is defined as an unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease associated with the use of the bendamustine therapy. Toxicity leads to side effects, which in these studies can broadly be classified as haematological</p>
	Stohr et al (2015)	8	direct		
	Michael et al (2010)	8	Direct		

**Use of Bendamustine plus or minus steroid for relapsed or refractory multiple myeloma (no comparator)**

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
					<p>(i.e. anaemia, leucopenia and thrombocytopenia), allergic, gastrointestinal reactions and infections.</p> <p>In the Stohr et al study (2015), 71% of patients (n=41) experienced severe (grade 3 or 4) anaemia, 16% (n=9) severe leucopenia and 21% (n=12) severe thrombocytopenia. However, it is reported that of the 30 patients with grade 4 anaemia, it only developed during or after bendamustine treatment in 6 patients (ie 24 had grade 4 anaemia prior to bendamustine treatment). Bendamustine dosage and whether patients had concomitant steroids did not influence the severity of the anaemia (p values not provided). A small number of patients suffered a mild allergy to bendamustine. Other side effects included mild fatigue, nausea, and vomiting.</p> <p>This suggests that severe (grade 3) and life-threatening (grade 4) levels of haematological toxicity are not uncommon in patients who have had bendamustine treatment for late stage multiple myeloma.</p> <p>This is an uncontrolled retrospective study. The lack of comparator in the study limits the strength of conclusions that can be drawn because, for example, many of the reported side effects may have been due to the illness itself and without a comparator group, we do not know how many were due to the bendamustine treatment. This is indicated, for example, by the relatively large proportion of patients that had grade 4 anaemia prior to bendamustine treatment. Additionally, the retrospective design of the study introduces the possibility of bias in the selection of patients for the study and in the outcome information obtained, as it is possible</p>

**Use of Bendamustine plus or minus steroid for relapsed or refractory multiple myeloma (no comparator)**

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
					that not all the relevant patients or information were included.

## 9 Literature Search Terms

Search strategy	
<p><b>P – Patients / Population</b> Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?</p>	Patients with relapsed multiple myeloma who are chemotherapy-refractory or chemotherapy-intolerant
<p><b>I – Intervention</b> Which intervention, treatment or approach should be used?</p>	Bendamustine +/- steroid
<p><b>C – Comparison</b> What is/are the main alternative/s to compare with the intervention being considered?</p>	Best supportive care (not including chemotherapy e.g. radiotherapy, antibiotics)
<p><b>O – Outcomes</b> What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.</p>	<p><u>Critical to decision-making:</u></p> <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Progression free survival</li> <li>• Overall response rate</li> <li>• Disease control rate</li> <li>• Adverse events</li> <li>• Quality of life (HRQoL)</li> <li>• Cost effectiveness</li> </ul> <p><i>Any other relevant outcome from included studies.</i></p> <p><u>Important to decision-making:</u></p>
Assumptions / limits applied to search	
<p><b><u>Inclusion criteria</u></b> <i>English language peer reviewed publications</i></p>	
<p><b><u>Exclusion criteria</u></b> <i>Abstracts. Conference papers. Papers published greater than 10 years ago. Letters and commentaries Uncontrolled studies</i></p>	

## 10 Search Strategy

We searched Medline, Embase and Cochrane Library limiting the search to papers published in England 2008 onwards. We excluded conference abstracts, commentaries and letters.

Search date: 9/03/2018

Embase search:

- 1 exp \*Multiple Myeloma/
- 2 myeloma\*.ti,ab.
- 3 1 or 2
- 4 \*Bendamustine/
- 5 (bendamustine or levact or treanda or bendeka).ti,ab.



6 4 or 5  
7 3 and 6  
8 limit 7 to (english language and yr="2008 -Current")  
9 conference\*.pt.  
10 8 not 9

## 11 Evidence Selection

- Total number of publications reviewed: 38
- Total number of publications considered potentially relevant: 9
- Total number of publications selected for inclusion in this briefing: 4

## 12 References

Damaj G. Malard F. Hulin C. Caillot D. Garidi R. Royer B. Marit G. Stoppa A.M. Banos A. Morineau N. Moreau P. Fitoussi O. Tiab M. Moreau P. 2012. Efficacy of bendamustine in relapsed/refractory myeloma patients: results from the French compassionate use program. *Leukemia & Lymphoma*, 53:632-634.

Kim SJ, Bang SM, Choi YS, Jo DY, Kim JS, Lee H, et al. Bendamustine in heavily pre-treated multiple myeloma patients: Results of a retrospective analysis from the Korean Multiple Myeloma Working Party. *Blood Research*. 2016;51(3):193-9

Leoni LM, Bailey B, Reifert J, Bendall HH, Zeller RW, Corbeil J, Elliott G, Niemeyer CC. 2008. Bendamustine (Treanda) displays a distinct pattern of cytotoxicity and unique mechanistic features compared with other alkylating agents. *Clin Cancer Res*, 14:309–17.

Michael M. Bruns I. Bolke E. Zohnren F. Czibere A. Safaian N. Neumann F. Haas R, Kobbe G. Fenk R. 2010. Bendamustine in patients with relapsed or refractory multiple myeloma. *Eur J Med Res* 15:13-19.

NHS England. 2018. Population, Intervention, Comparator and Outcomes (PICO): Bendamustine for relapsed multiple myeloma. URN 1608. March 2018.

NHS England. 2018 National Cancer Drugs Fund List ver. 1.80 May 2018.

NHS Choices 2018, Multiple Myeloma (<https://www.nhs.uk/conditions/multiple-myeloma/>) accessed 3/5/2018

National Institute for Health and Care Excellence. NICE Guidelines, 2016, Myeloma diagnosis and management. (<https://www.nice.org.uk/guidance/ng35/chapter/recommendations#managing-newly-diagnosed-myeloma>); (<https://www.nice.org.uk/guidance/ng35/chapter/Recommendations#managing-relapsed-myeloma>) accessed 3/5/2018

Stohr E. Schmeel F.C. Schmeel L.C. Hanel M. Schmidt-Wolf I.G.H. 2015. Bendamustine in heavily pre-treated patients with relapsed or refractory multiple myeloma. *J Cancer Res Clin*

*Oncol*, 141:2205-2212.

Strumberg D. Harstrick A. Doll K. Hoffmann B. Seeber S. 1996. Bendamustine hydrochloride activity against doxorubicin resistant human breast carcinoma cell lines. *Anticancer Drugs*, 7:415–21.