PMB definition guideline for Multiple myeloma

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Disclaimer:

The multiple myeloma benefit definition guideline has been developed for majority of standard patients and is aligned with best practice. These benefits may not be sufficient for outlier patients. Therefore, regulation 15h may be applied for patients who are inadequately managed by the stated benefits. The benefit definition does not describe specific in-hospital management. However, these interventions form part of care and are prescribed minimum benefits. Supportive medication for all haematology oncology conditions is detailed in a separate guideline available here.

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Abbreviations

ASCT	Autologous stem cell transplant
CVAD	Cyclophosphamide, Vincristine, Doxorubicin and Dexamethasone
DCEP	Dexamethasone, Cyclophosphamide, Etoposide and Cisplatin
DTPs	Diagnosis Treatment Pairs
FLC	Free light chain
IFRT	Involved-field radiation therapy
IMWG	International Myeloma Working Group
MDEs	Myeloma defining events
PMBs	Prescribed Minimum Benefits
VTD-PACE	Bortezomib, Thalidomide, Dexamethasone, Cisplatin, Doxorubicin, Cyclophosphamide and Etoposide

1. Introduction

1.1. The legislation governing the provision of the Prescribed Minimum Benefits (PMBs) is contained in the Regulations enacted under the Medical Schemes Act, No. 131 of 1998 (the Act). With regards to some of the Diagnosis Treatment Pairs (DTPs), medical scheme beneficiaries find it difficult to be fully aware of their entitlements in advance. In addition, medical schemes interpret these benefits differently, resulting in a lack of uniformity of benefit entitlements.

1.2. The benefit definition project is undertaken by the CMS with the aim of defining the PMB package, as well as to guide the interpretation of the PMB provisions by relevant stakeholders.

2. Scope and purpose

2.1. This is a recommendation for the diagnosis, treatment and care of individuals with multiple myeloma in any clinically appropriate setting as outlined in the Medical Schemes Act.

2.2. The purpose is to provide detailed clarification in respect of benefits and entitlements to members and beneficiaries of medical schemes.

Table 1: Possible ICD10 codes for patients with multiple myeloma in the curative and palliative setting

DTP code	ICD 10 code	ICD10 code description
910 S: Multiple myeloma and chronic leukaemias	C90.0	Multiple myeloma
260S - # Imminent death regardless of diagnosis	Z51.5	Palliative care

3. Epidemiology

Multiple myeloma (MM) is a plasma cell dyscrasia that accounts for approximately 10% of haematological malignancies and 1% of all cancers in the USA (Fazel and Bassa, 2019). MM is usually preceded by an asymptomatic premalignant condition known as monoclonal gammopathy of undetermined significance (MGUS). MGUS is present in 3 - 4% of people >50 years of age and 5% of people >70 years of age. The risk of progression to MM is 1% per year. Smoldering multiple myeloma (SMM) is a more advanced premalignant phase between MGUS and MM. The risk of progression from SMM to MM is 10% per year in the first 5 years, followed by 3% per year in the next 5 years, and 1.5% per year,

thereafter. This rate of progression is influenced by underlying cytogenetic abnormalities. The spectrum of presentation of MM varies from asymptomatic to aggressive disease, with the most aggressive presentation being that of a plasma cell leukemia (PCL).

In South Africa, multiple myeloma accounts for approximately 0.83% of all histologically diagnosed cancers, with a slight male predominance. Most of the patients were diagnosed in their 70s, with approximately 18% diagnosed below 50 years of age. According to the 2016 National Cancer Registry report, which was updated in 2020, table 2 and 3 below gives a breakdown of cancers by gender and ethnicity.

Table 2: Prevalence of MM in females in South Africa

Females	Actual number of cases	Percentage of all cancers
All females	166	0.39%
Asian females	10	0.24%
Black females	92	0.45%
Coloured females	18	0.39%
White females	53	0.33%

Table 3: Prevalence of MM in males in South Africa

Males	Actual number of cases	Percentage of all cancers
All males	172	0.44%
Asian males	5	0.51%
Black males	76	0.58%
Coloured males	18	0.39%
White males	73	0.35%

4. Diagnostics and risk stratification work-up

4.1. **Laboratory tests**

4.1.1. The following tests are PMB level of care for multiple myeloma (NCCN, 2020; Fazel & Bassa, 2019) :

Baseline tests / initial workup

- Full blood count, differential, platelet count
- Peripheral blood smear
- CRP
- Clotting profile (Includes PTT/INR)
- Serum BUN/creatinine, electrolytes, albumin, calcium, serum uric acid
- Creatinine clearance (calculated or measured directly)
- Serum quantitative immunoglobulins (IgG, IgA, IgM), serum protein electrophoresis
- Serum immunofixation electrophoresis
- 24-h urine for total protein, urine protein electrophoresis, and urine immunofixation electrophoresis (if serum free light chains is not available)
- Serum free light chain (FLC) assay and free light chain ratio. If unavailable, Bence Jones protein can be used
- Haematinics – Iron, Vit B12 and Folate
- Biopsy for histology if extramedullary mass (plasmacytoma) is present

Confirmatory tests

- Unilateral bone marrow aspirate and biopsy, including immunohistochemistry and/or multi-parameter flow cytometry and cytogenics.

Risk stratification tests

- Full liver function tests including lactate dehydrogenase
- Beta-2 microglobulin
- Plasma cell FISH panel on bone marrow [del 13, del 17p13, t(4;14), t(11;14), t(14;16), t(14;20), 1q21 amplification, 1p deletion]

4.2. **Imaging radiology**

4.2.1. Imaging is also used for the confirmation of the diagnosis for multiple myeloma.

4.2.2. Whole body imaging is PMB level of care for those diagnosed with multiple myeloma. The choice between skeletal survey, whole body MRI, PET-CT or low dose whole body CT is at the discretion of the treating doctor.

4.2.3. When functional imaging is employed (MRI or PET/CT) these should be repeated at the end of induction therapy to provide an additional assessment of response. These modalities should also be used in the relapsed setting.

4.2.4. MRI is the modality of choice for imaging of the spine and is PMB level of care. MRI spine or pelvis should be performed in those with suspected cord compression or other nerve impingement. If MRI cannot be performed, then a CT can be used (London Cancer Alliance, 2020).

4.2.5. In a study that compared whole body multi-detector CT and conventional radiography in the staging of multiple myeloma, multi-detector CT showed a significantly higher sensitivity and diagnostic confidence in the detection of osteolysis compared to conventional radiography, particularly in the vertebral column, pelvic skeleton and the thoracic cage. There were more lesions of any size detected with a higher level of confidence and demonstration of extra-osseous findings by multi-detector CT (Krӧpil, et al. 2008).

4.2.6. A prospective study comparing conventional x-rays to CT scans and PET-CT, found that low-dose CT of the axial skeleton diagnose significantly more patients with osteolysis than X-rays. Low dose CT is recommended as a standard procedure for detection of osteolytic lesions at baseline assessments for multiple myeloma. It will also provide additional information regarding paramedullary and extramedullary involvement and risk of spinal cord compression (Hinge, et al. 2016).

5. Risk classification of multiple myeloma

5.1. Traditionally, the diagnosis of multiple myeloma has required the presence of end-organ damage known as the CRAB criteria, which includes increased calcium level, renal dysfunction, anaemia, and destructive bone lesions. International Myeloma Working Group (IMWG) has revised the criteria and in addition to the classic CRAB features, the revised criteria have three myeloma defining events (MDEs).

5.2. The presence of at least one of these markers is considered sufficient for a diagnosis of multiple myeloma, regardless of the presence or absence of symptoms or CRAB features. Each of these markers has been shown in two or more independent studies to be associated with an approximately 80% or higher risk of developing myeloma-related organ damage within two years.

5.3. The new definition of Multiple myeloma is clonal bone marrow plasma cells>10% or biopsy-proven bony or extra medullary plasmacytoma and any one of the more of the following CRAB features and myeloma-defining events.

Table 3: CRAB and MDE criteria

CRAB features	One or more of the following biomarkers of malignancy (MDE)
• **C**alcium >0.25mmol/L (>1mg/dL) higher than the upper limit of normal or >2.75mmol(>11mg/dL) • **R**enal insufficiency (creatinine>2mg/dL)[>177micromol/L] or creatinine clearance <40mL/min • **A**nemia (haemoglobin <10g/dL or haemoglobin >2g/dL below the lower limit of normal) • **B**one lesions: One or more osteolytic bone lesions on skeletal radiography, CT, or FDG PET/CT	• Clonal bone marrow plasma cells ≥ 60% • Involved: uninvolved serum free light chain ratio ≥100 and involved FLC concentration 10mg/dL or higher • >1 focal lesion on MRI studies ≥ 5mm[1]

6. Management of multiple myeloma

6.1. A randomised phase III study that evaluated the effect of Thalidomide before and after high dose Melphalan and ASCT in patients with recently diagnosed multiple myeloma, showed that Thalidomide treatment had an overall survival advantage as compared with classical cytotoxic drugs and interferon alfa.

6.2. A multicentre phase III randomised trial looked at consolidation with Cyclophosphamide and Dexamethasone plus Lenalidomide versus high dose Melphalan and autologous stem cell transplant (ASCT). The results showed that high dose Melphalan and ASCT improves progression-free survival and overall survival at a cost of increased but manageable adverse events. High dose melphalan and ASCT remains the preferred therapeutic option in transplant eligible patients with newly diagnosed multiple myeloma (Gay, et al. 2015).

6.3. An updated network meta-analysis assessed whether the addition of bisphosphonates improved overall survival, progression free survival and skeletal-related morbidity. Bisphosphonates are PMB level of care as the findings are evident that the use of bisphosphonates reduces pathological vertebral fractures, skeletal related events and pain (Mhaskar, et al. 2017).

6.4. A study that looked at different treatment options CVAD (Cyclophosphamide, Vincristine, Doxorubicin and Dexamethasone), DCEP (Dexamethasone, Cyclophosphamide, Etoposide and Cisplatin) and VTD-PACE

(Bortezomib, Thalidomide, Dexamethasone, Cisplatin, Doxorubicin, Cyclophosphamide and Etoposide) for patients with recurrent/refractory multiple myeloma. The three salvage regimens demonstrated no significant differences in outcomes among patients with recurrent/refractory multiple myeloma. The more aggressive regimen (VTD-PACE) did not demonstrate superior disease response or survival (Griffin, et al. 2015)

6.5. A summary of PMB recommendations for multiple myeloma is given in table 4 below.

Recommendation for Bortezomib, Bendamustine and Lenalidomide

6.6. A randomised phase III study demonstrated that among previously untreated multiple myeloma patients, induction therapy with Bortezomib plus Dexamethasone significantly improved both post-induction and post-transplantation rates of complete response/near complete response when compared to Vincristine, Doxorubicin and Dexamethasone. It was equally effective in patients with high risk multiple myeloma, and those with poor risk cytogenic abnormalities (Harousseau, et al. 2010)

6.7. A systematic review and meta-analysis assessed the effects of Bortezomib treatment in comparison to other therapies. The review found that there is a clear benefit in overall and progression –free survival in favour of Bortezomib. Patients treated with Bortezomib also had overall response rate and complete response rates that were significantly higher than in control groups. Patients treated with Bortezomib also had significantly greater risk of thrombocytopenia, neutropenia, gastrointestinal toxicities, peripheral neuropathy, infection and fatigue (Scott, et al. 2016).

6.8. Bortezomib-based induction is the current standard of care in these patients and Lenalidomide is the preferred choice for maintenance therapy since it improves progression free survival and overall survival and has less toxicity than Thalidomide (van de Donk, et al. 2018).

6.9. A phase III study compared Bendamustine and Prednisone to standard Melphalan and Prednisone treatment in previously untreated patients with multiple myeloma. The results showed 75% overall response rate in the Bendamustine group compared to 70% in the Melphalan group. A significantly higher number of patients treated with Bendamustine achieved a complete remission than did patients receiving Melphalan (32 vs 13%, p=0.007). The maximum response was achieved more rapidly in patients with Bendamustine than those on Melphalan. Bendamustine treatment was superior to melphalan treatment in terms of complete remission, time to treatment failure, cycles needed to achieve maximum remission and quality of life (Pœnisch, et al. 2006).

6.10. A phase II study of Bendamustine, Bortezomib and Dexamethasone in the first line treatment of multiple myeloma in patients who are not eligible for high dose chemotherapy resulted in an overall response rate of 91% and complete response of 9%. The most common grade 3 or 4 adverse events were fatigue and neuropathy, but the combination was found to be efficacious and tolerable in this patient population (Berdeja, et al. 2017).

6.11. A phase II prospective study looked at Bendamustine and Melphalan conditioning of second autologous stem cell transplantation in previously untreated multiple myeloma patients. The patients underwent high dose melphalan as conditioning for first autologous stem cell transplantation and responding patients underwent a second autologous stem cell transplantation following Bendamustine. Overall response rate was 81.2% after the first transplant and 90.6% after the second and complete response rates were 46.8% and 62.5% respectively. Bendamustine is feasible as the conditioning regimen for the second autologous stem cell transplantation in multiple myeloma patients (Martino, et al. 2016).

6.12. Bendmustine and Lenalidomide are not listed on the NEML and although not considered PMB level of care, schemes are encouraged to fund when clinically appropriately based on the clinical benefit and the availability of generic alternatives.

6.13. Bortezomib is recommended as PMB level of care for multiple myeloma on a case by case basis.

Table 4: Summary of medicine recommendations for multiple myeloma

Medicine	CMS Recommendation
• Melphalan • Cyclophosphamide • Thalidomide • Doxorubicin • Vincristine • Etoposide • Cisplatin • Corticosteroids • Bisphosphonates IV • Bortezomib	**PMB level of care**
• Bendamustine	**PMB level of care at the discretion of the scheme** Schemes are encouraged to consider funding as there is very good evidence of clinical benefit.
• Lenalidomide	**PMB level of care at the discretion of the scheme.** There are generic alternatives available and schemes are encouraged to consider funding lenalidomide when deemed cost effective.

7. Transplant

7.1. CMS is cognisant that stem cell transplant is not listed on the DTP for multiple myeloma, however clinical evidence has evolved, and the MSA stipulates that clinically appropriate care that is evidence based and

cost effective should be provided to beneficiaries. Autologous stem cell transplant is the prevailing level of care in the state sector for multiple myeloma patients and is recommended as PMB level care for patients who are clinically eligible.

7.2. Allogeneic stem cell transplant is not PMB level of care for multiple myeloma.

8. Radiation therapy

8.1. Radiation therapy is PMB level of care for spinal cord compression and pain control for confirmed multiple myeloma patients.

8.2. A retrospective study analysed 237 patients' response to radiotherapy and found that radiotherapy alone provides excellent response rates, functional outcomes such as post radiotherapy ambulation (overall ambulation at 88%) and local control of spinal cord compression (at three years follow up 82% local control) in patients with malignant spinal cord compression from myeloma (Rades, et al. 2016).

8.3. A retrospective analysis from a single institution assessed effects of radiotherapy in the treatment of multiple myeloma. The study revealed that palliative radiotherapy mostly results in pain relief without significant toxicity. The data showed that higher doses of radiation (30-36 Gy) are associated with improved pain relief. Younger patients may need higher radiation doses as the data shows analgesic effects of radiotherapy seemed to be less pronounced in these patients. The likelihood of recalcification after radiotherapy is also increased at higher doses of radiation (>40 Gy) and this should be taken into consideration if recalcification is thought to be necessary to lower the risk of fractures (Matuschek, et al. 2015).

8.4. Involved-field radiation therapy (IFRT) is PMB level of care for plasmacytomas.

9. Supportive treatment

9.1. Supportive treatment for multiple myeloma is PMB level of care when clinically indicated.

9.2. Guidance on supportive treatment is available here.

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