PMB definition guideline for Myeloproliferative neoplasms
Version 1: 24 December 2020
Disclaimer:
The myeloproliferative neoplasms 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 such as theatre, anaesthetist drugs and supportive medication. 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.

CMS is cognisant of the criteria for stem cell transplantation as stipulated in the PMB regulations, however clinical evidence has changed, and clinical best practice should prevail. The following should be noted:

- Related or unrelated donors on the local registry should be considered as there is no difference in outcome data for patients transplanted from a matched family donor or a matched unrelated donor.
- There should not be any age restrictions.
Acknowledgements

The Council for Medical Schemes (CMS) would like to acknowledge all stakeholders who assisted in drafting this document, including participant haematologists, oncologists, pathologists, patient advocacy groups, funders and administrators.

Specifically, the CMS acknowledges the following clinical experts for their insights during the drafting of this document:

Dr Estelle Verburgh  Dr Leonard Mutema  Dr Sheynaz Bassa
Dr Hannes Koorhof  Dr Lucile Singh  Dr Theo Gerderner
Dr H-T Wu  Dr Mariain Kruger  Dr Yasmin Goga
Dr Jacqueline Thompson  Dr Nokwanda Zuma  Professor Moosa Patel
Dr Johani Vermuelen  Dr Pelisa Ford  Professor Paul Ruff
Dr Justin du Toit  Dr David Brittain

The contributions on member entitlements of the following individuals from professional bodies, patient advocacy groups, medical schemes and administrators were immensely valuable in drafting this document:

Dr Eric Hefer  Ms Caroline Rich
Dr Jo Samsononwicz  Ms Edelweiss Potgieter
Dr Lindiwe Mbekeni  Ms Kim Cardwell
Dr Morwesi Mahlangu  Ms Lauren Pretorius
Dr Samukeliso Dube  Ms Shelley McGee

Dr John Mathabathe is also acknowledged by the CMS for his assistance in the drafting of this document.
Table of Contents

1. Introduction..................................................................................................................................................6
2. Scope and purpose.........................................................................................................................................6
3. Classification and description of MPNs.......................................................................................................6
   3.1 Classification..........................................................................................................................................6
4. Epidemiology................................................................................................................................................7
5. Diagnostics and work up...............................................................................................................................7
   5.1 Laboratory tests......................................................................................................................................7
   5.2 Genetic testing, biopsy and pathology.....................................................................................................8
   5.3 Imaging...................................................................................................................................................9
6. Risk classification of MPNs..........................................................................................................................9
7. Management of myeloproliferative neoplasms..........................................................................................11
8. Radiation therapy..........................................................................................................................................13
9. Procedures..................................................................................................................................................14
10. Transplant..................................................................................................................................................14
11. Supportive treatment....................................................................................................................................15
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMBs</td>
<td>Prescribed Minimum Benefits</td>
</tr>
<tr>
<td>DTPs</td>
<td>Diagnosis Treatment Pairs</td>
</tr>
<tr>
<td>MPN</td>
<td>Myeloproliferative Neoplasms</td>
</tr>
<tr>
<td>PV</td>
<td>Polycythemia Vera</td>
</tr>
<tr>
<td>CML</td>
<td>Chronic Myeloid Leukemia</td>
</tr>
<tr>
<td>PMF</td>
<td>Primary Myelofibrosis</td>
</tr>
<tr>
<td>ET</td>
<td>Essential Thrombocythemia</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate Dehydrogenase</td>
</tr>
<tr>
<td>HLA</td>
<td>Human Leucocyte Antigen</td>
</tr>
<tr>
<td>HSCT</td>
<td>Hematopoietic Stem Cell Transplantation</td>
</tr>
<tr>
<td>FISH</td>
<td>Fluorescent In-Situ Hybridization</td>
</tr>
<tr>
<td>DIPSS</td>
<td>Dynamic International Prognostic Scoring System</td>
</tr>
</tbody>
</table>
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 myeloproliferative neoplasms (MPN) in any clinically appropriate setting as outlined in the Medical Schemes Act.

2.2. Myeloproliferative neoplasms included in this guideline are polycythaemia vera (PV), essential thrombocythaemia (ET), and primary myelofibrosis (PMF).

2.3. 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 myeloproliferative neoplasms in the curative and palliative setting |
|---|---|---|---|
| DTP code | ICD 10 code | ICD10 code description |
| 910 S: Multiple myeloma and chronic leukaemias | C94.6 | Myelodysplastic and myeloproliferative disease, not elsewhere classified |
| 260S - # Imminent death regardless of diagnosis | Z51.5 | Palliative care |

3. **Classification and description of MPNs**

3.1. **Classification**

3.1.1. MPNs are a group of chronic myeloid disorders characterised by stem cell-derived clonal myeloproliferation. According to the 2016 World Health Organization (WHO) classification system for
tumours of the haematopoietic and lymphoid tissues, the following subcategories are included as part of myeloproliferative neoplasms (Barbui, et al. 2018):

- Chronic myeloid leukaemia (CML)
- Chronic neutrophilic leukaemia
- Polycythaemia vera (PV)
- Primary myelofibrosis (PMF)
- Essential thrombocythemia (ET)
- Chronic eosinophilic leukaemia-not otherwise specified
- MPN, unclassifiable (MPN-U)

3.1.2. Although there are seven types of MPNs, this guideline will cover the three classic types namely PV, ET and PMF.

3.1.3. CML is different to the other forms of MPN as it is characterised by the Philadelphia chromosome, which is discussed in a separate document available here.

3.1.4. Although the other subtypes of MPNs are not currently included in this guideline; diagnosis, treatment and care for all forms of MPNs constitutes PMB level of care.

4. Epidemiology

4.1. As indicated above with the WHO classification, MPNs are a heterogeneous group of rare diseases.

4.2. This is confirmed by the pooled incidence from a systematic review of 34 cohort studies which reports combined annual incidence rates for PV, ET, and PMF as 0.84, 1.03, and 0.47 per 100,000 respectively. The calculated pooled incidence rates do not reflect MPN incidence across the globe due to the high unexplained heterogeneity (Titmarsh, et al. 2014).

4.3. No epidemiological data is available for all forms of MPNs in the 2016 National Cancer Registry (updated April 2020) for South Africa, most likely because it is a very rare form of leukaemia.

5. Diagnostics and work up

5.1. Laboratory tests

5.1.1. Initial workup for diagnosis of the MPNs includes the following (NCCN,2019)

- Peripheral blood smear
- Comprehensive metabolic panel including uric acid, lactate dehydrogenase, and liver function tests
- Iron studies (serum iron, transferrin saturation, ferritin)
- Serum erythropoietin level (where JAK-2V617F mutation is negative and PV is suspected)
- Basic coagulation screening, including prothrombin time, activated partial thromboplastin time
5.2. Genetic testing, biopsy and pathology

5.2.1. Genetic testing is important in identifying patients at risk for requiring treatment with chemotherapy or those at risk for developing major cardiovascular complications.

5.2.2. CML is the only MPN that is characterised by the Philadelphia chromosome (BCR-ABL), hence it has a unique pathogenesis and treatment.

5.2.3. Fluorescent in-situ hybridization (FISH) analysis or real time Polymerase Chain Reaction (PCR) on peripheral blood is done to detect BCR-ABL1 transcripts and exclude the diagnosis of CML (NCCN, 2019).

5.2.4. The three driver mutations for BCR-ABL negative MPNs are JAK2, CALR and MPL. The most commonly recognised mutation is JAK2 V617F, which is present in more than 90% of patients with PV and approximately half of those with PMF or ET. Mutations within the MPL gene and CALR H have also been identified in ET and PMF (Gerds, 2016).

5.2.5. Human leucocyte antigen (HLA) typing should be performed for patients whom allogenic hematopoietic stem cell transplantation (HCT) would be considered.

5.2.6. Genetic tests for MPNs are PMB level of care and tests should be done in a sequential order as the "driver mutations" are often mutually exclusive, meaning that if one is present the others are absent.

5.2.7. Table 2 below may be used as a guide for the sequence of tests. For example, if JAK2 V617F mutation is negative for ET, testing for MPL and CALR mutations testing may be performed sequentially in the specific order.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polycythemia Vera</th>
<th>Essential Thrombocytethemia</th>
<th>Primary Myelofibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK2</td>
<td>97%</td>
<td>50 - 60%</td>
<td>50 - 60%</td>
</tr>
<tr>
<td>CALR</td>
<td>3 - 10%</td>
<td>3 - 10%</td>
<td></td>
</tr>
<tr>
<td>MPL</td>
<td>33%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Unmutated JAK2, CALR, MPL</td>
<td>10 - 15%</td>
<td>10 - 15%</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Percentage of gene mutations among patients with Philadelphia chromosome-negative myeloproliferative neoplasms (Gerds, 2016).
5.3. Imaging

5.3.1. Chest X-ray, abdominal ultrasound, echocardiogram and electrocardiogram (ECG) are PMB level of care.

5.3.2. Abdominal ultrasound or computerised tomography (CT) scan for evaluation of spleen may be considered when transformation to myelofibrosis is suspected based on clinical or haematological criteria.

5.3.3. All other imaging is PMB level of care on motivation.

6. Risk classification of MPNs

6.1. The classification of MPNs is based on age, history of vascular complications and thrombocytosis (Rumi and Cazzola, 2017).

6.2. The treatment approach is determined and tailored based on the risk stratification.

6.3. At the time of publication, the South African oncology guidelines, that is, South African Oncology Consortium (SAOC) and Icon oncology did not explicitly have any risk classification for the recommended therapeutic interventions.

6.4. For PV, there are two categories – low and high risk which are dependant on the risk of thrombotic complications.

   - Low risk - age < 60 years old and no prior thrombosis or disease-associated bleeding event
   - High risk - age ≥ 60 years old and/or prior thrombosis or disease-associated bleeding event

Primary myeloﬁbrosis (PMF)

6.5. Various guidelines refer to different risk scoring for PMF. The Dynamic International Prognostic Scoring System (DIPSS) and DIPSS-Plus are used by multiple international guidelines to reassess the risk stratification during the course of disease, for purposes of guiding therapy.

6.6. The DIPSS includes five parameters that impact survival (table 3) and the total score determines the four prognostic risks groups which are tabulated in table 4 below.

Table 3: The DIPSS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 years</td>
<td>1</td>
</tr>
<tr>
<td>Anemia: hemoglobin &lt; 10 g/dL</td>
<td>2</td>
</tr>
<tr>
<td>Circulating blasts: ≥ 1%</td>
<td>1</td>
</tr>
<tr>
<td>Constitutional symptoms (i.e., weight loss &gt; 10%, night sweats, or fevers)</td>
<td>1</td>
</tr>
<tr>
<td>Leukocytosis: WBC &gt; 25 x 10⁹/L</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 4: Risk groups and associated prognostic outcomes

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Points</th>
<th>Survival, median yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>1-2</td>
<td>14.2</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>3-4</td>
<td>4</td>
</tr>
<tr>
<td>High</td>
<td>5-6</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BP-MF, incidence / 100 pt-yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.6</td>
</tr>
</tbody>
</table>

Essential thrombocytemia (ET)

6.7. As with the other two MPNs discussed earlier, treatment for ET is based on risk stratification. ET patients are classified as low, intermediate and high risk.

- Low-risk patients - younger than 60 years of age, no history of thrombosis or cardiovascular risk factors, and platelet counts ≤1,500 x 10^9/L.
- High-risk patients - older than 60 years of age or with a history of thrombosis.
- Intermediate-risk patients - patients not falling into either of the above groups

6.8. The risk stratification for the MPNs is summarised in table 5 below.

Table 5: Risk classification of MPNs

<table>
<thead>
<tr>
<th>Risk stratification</th>
<th>PV</th>
<th>PMF</th>
<th>ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td></td>
<td></td>
<td>Low risk</td>
</tr>
<tr>
<td>High-risk</td>
<td></td>
<td></td>
<td>Intermediate risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermediate risk1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermediate risk 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High-risk</td>
</tr>
</tbody>
</table>

7. Management of myeloproliferative neoplasms

7.1. The therapeutic goals for patients with myeloproliferative neoplasms are to reduce the risk of thrombosis and haemorrhage, to prevent the transformation to the blast phase and acute myeloid leukaemia which are associated with poorer prognosis (Spivak, 2017).

Antiplatelet therapy

7.2. Low-dose acetylsalicylic acid (aspirin) is PMB level of care for patients with MPNs (Alvarez-Larrán & Besses, 2014).
7.3. The use of aspirin for ET and PMF is based on the European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP) trial of patients with PV in which low dose aspirin was shown to be effective at reducing thrombotic events and alleviate vasomotor (microcirculatory) symptoms (Landolfi, et al. 2004; Finazzi, 2004).

7.4. In patients with PV, low dose aspirin may be used in combination with phlebotomy as the first line option (Hatalova, et al. 2018).

7.5. Clopidogrel is PMB level of care for patients who are intolerant or resistant to aspirin.

**Hydroxyurea**

7.6. Hydroxyurea, an antimetabolite that slows DNA synthesis by inhibiting ribonucleoside reductase, is one of the most commonly used first line cytoreductive agents for MPNs (Choi et al., 2015)

7.7. There is no consensus in the literature and also no definitive evidence for or against leukemogenic risk for patients with PV but risk may appear after prolonged exposure, hence a conservative approach of considering alternative treatments may be reasonable in young patients and patients previously treated with other myelosuppressive agents (Vannucchi, et al. 2015).

7.8. The results from randomized clinical trials in patients with ET have been extrapolated to patients with PV (Passamonti, 2012). Hydroxyurea is PMB level of care for PV when deemed clinically appropriate (e.g. high risk, low risk who are phlebotomy intolerant, severe/progressive symptoms, cardiovascular risk factors).

7.9. For PMF, hydroxyurea is PMB level of care when clinically indicated and this may include patients with low-risk disease in need of therapy or those with intermediate-1 disease who do not have highly symptomatic splenomegaly.

7.10. About 25% of patients are reported to develop resistance or intolerance to hydroxyurea (Radia & Geyer, 2015).

7.11. The criteria for resistance or intolerance to hydroxyurea in patients with ET requires at least one of the following:

- platelet count > 600 × 10⁹/L after 3 months of at least hydroxyurea ≥ 2 g/day (2.5 g/day in patients > 80 kg)
- platelet count > 400 × 10⁹/L with white blood count < 2.5 × 10⁹/L or haemoglobin < 10 g/dL at any dose of hydroxyurea
- leg ulcers or other unacceptable mucocutaneous manifestations at any dose of hydroxyurea
- hydroxyurea-related fever

**Anagrelide**

7.12. Anagrelide is not recommended as a 1st line option. For the patients with ET and PV who meet criteria stated in 7.11 above, anagrelide is PMB level of care.
7.13. Anagrelide was found to be non-inferior as a platelet-lowering alternative for ET patients intolerant to hydroxyurea in the ANAHYDRET Study (Gisslinger, et al. 2013).

**Busulfan**


7.15. In a retrospective analysis, the efficacy of busulfan in patients with advanced PV or ET refractory or intolerant to hydroxyurea was assessed in 36 patients (PV n = 15, ET n = 21) treated for a median of 256 days (Alvarez-Larrán, et al. 2014).

7.16. Busulfan was found to be an effective option for elderly patients with PV or ET who fail to respond to hydroxyurea (Barbui, et al. 2018)

7.17. Although Busulfan is rarely used for the treatment of the MPN nowadays, it is PMB level of care when clinically indicated.

**Interferons**

7.18. Interferon-alpha may be preferred first-line therapy for younger patients due to unknown leukemogenic risk with long-term hydroxyurea. It is recommended as a first-line therapy option in patients with high-risk PV in the following scenarios (Vannucchi, et al. 2015):

- resistant to, or are intolerant of hydroxyurea
- childbearing potential/ during pregnancy

7.19. Interferon therapy is PMB level of care, however, it is no longer commercially available in South Africa.

**Thalidomide**

7.20. In a case series of 44 patients with PMF, thalidomide was reported to provide a response to varying degrees. Of 41 evaluable patients (Thomas, et al. 2006)

- 41% (n=17) had a response.
- 10% (n=4) had a complete response (without reversal of bone marrow fibrosis)
- 10% (n=4) had a partial response
- 21% (n=9) had hematologic improvements in anemia, thrombopenia, and/or splenomegaly

7.21. Thalidomide is PMB level of care for PMF and may be useful for management of

- myelofibrosis-related anemia
- splenomegaly
thrombocytopenia

Imatinib
7.22. Imatinib is not PMB level of care for BCR-ABL negative MPNs.
7.23. The evidence for the use of imatinib in PV is based on an uncontrolled trial and a case series of 11 patients. In those studies, imatinib was shown to reduce phlebotomy, white blood cell count, and platelet count in patients with PV (Cortes & Kantarjian, 2004).

Ruxolitinib
7.24. As stated earlier, the most commonly recognized mutation for the MPNs under discussion are JAK2 V617F, which is present in more than 90% of patients with PV and approximately half of those with PMF or ET.
7.25. Ruxolitinib, a JAK inhibitor, has shown efficacy in treatment of patients with ET resistant or refractory to hydroxyurea, intermediate and high-risk PMF, or patients with PV having inadequate response to or who are intolerant of hydroxyurea. In the COMFORT I and II trials, Ruxolitinib showed efficacy in reducing spleen size and improving symptoms in patients with PMF (Tefferi, 2017)
7.27. There is an unmet need for the treatment of intermediate and high risk PMF; and there is evidence which shows a survival benefit in this category of patients. Although Ruxolitinib is not currently PMB level of care, CMS encourages the funding thereof for the subset of patients who will benefit.

8. Radiation therapy
8.1. Radiation is indicated as PMB level of care for symptomatic hypersplenism (splenomegaly), extramedullary hemopoieses.
8.2. In a literature review and retrospective analysis evaluating the effectiveness of low dose radiation therapy for symptomatic splenomegaly in malignant and benign diseases, low doses of radiation therapy were effective with low rate of side effects. The splenic pain and abdominal discomfort improved (de La Pinta, et al. 2017).

9. Procedures
9.1. Therapeutic phlebotomy is considered the mainstay of PV treatment, improving overall and thrombosis-free survival (Assi & Baz, 2013; Hatalova, et al. 2018).
9.2. Splenectomy has been associated with significant mortality and usually offered as a palliative approach after drug treatments fail. Careful selection for splenectomy is required. Splenectomy for patients with PV and PMF may be indicated for the following (Logan, et al. 2009).

- painful splenomegaly with compressive symptoms
- refractory haemolytic anaemia
- severe thrombocytopenia and frequent red blood cell transfusions
- symptomatic portal hypertension
- portal-splenic-mesenteric thrombosis

9.3. For patients with ET, splenectomy is rarely performed due to the mortality risk (Barbui, et al. 2018).

9.4. Splenectomy is PMB level of care for MPNs when the benefit outweighs the risk. A motivation from the treating provider may be required.

10. Transplant

10.1. The only treatment associated with possible cure is allogeneic HSCT. However, it is associated with significant morbidity and mortality and used only selectively.

10.2. HSCT from an HLA-matched sibling, matched unrelated or alternative (including haploidentical or cord blood) donor is a preferred approach for treating select patients particularly those with high-risk disease (Luznik, et al. 2008; Scott, et al. 2006; Wallen, et al. 2005).

10.3. In patients who relapse after a prolonged remission following the first transplant, a second transplant may be considered.

10.4. Azacitidine, Decitabine or other therapies may be used as a bridge to transplantation.

10.5. The following medicines are PMB level of care for transplant:

- Fludarabine
- Busulfan
- Cyclophosphamide
- Anti-thymocyte globulin (ATG)
- Melphalan
- Cyclosporin
- Tacrolimus
- Methotrexate
- Etoposide
- Thalidomide
- Imatinib
• Ruxolitinib – indicated as 2nd line for graft vs host disease

11. Supportive treatment
   11.1. Supportive treatment for MPNs is PMB level of care when clinically indicated.
   11.2. Guidance on supportive treatment is available here.
References


Mascarenhas, J. et al. (2018) ‘Results of the Myeloproliferative Neoplasms - Research Consortium (MPN-RC) 112 Randomized Trial of Pegylated Interferon Alfa-2a (PEG) Versus Hydroxyurea (HU) Therapy for the Treatment of High Risk Polycythemia Vera (PV) and High Risk Essential Thrombocythemia (ET)’, *Blood*. American Society of


