PMB definition guideline for cutaneous T-cell lymphoma
Version 1

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Disclaimer:

The cutaneous T-cell lymphoma *benefit definition guideline has been developed for the 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

CBCL	Cutaneous B-cell lymphoma
CR	Complete Response
CT	Computed Tomography
CTCL	Cutaneous T-cell Lymphoma
DTPs	Diagnosis Treatment Pairs
ECP	Extracorporeal Photophoresis
FBC	Full Blood Count
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
FMF	Folliculotropic Mycosis Fungoides
INR	International Normalized Ratio
LCT	Large Cell Transformation
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
MF	Mycosis Fungoides
ORR	Overall Response Rate
PCL	Primary Cutaneous Lymphomas
PMBs	Prescribed Minimum Benefits
PR	Partial Response
PTT	Partial Thromboplastin Time
SS	Sezary Syndrome
TCR	T-Cell antigen Receptor
TNMB	Tumour-Nodes-Metastasis-Blood
TSEBT	Total Skin Electronic Beam Therapy
U&E	Urea and Electrolytes

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 cutaneous T-cell lymphoma (CTCL), specifically mycosis fungoides and Sezary syndrome, in any clinically appropriate setting as outlined in the Medical Schemes Act.
2.2. This document will only focus on the two common types of CTCL; however, all forms of cutaneous lymphoma are considered a PMB.
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 CTCL in the curative and palliative setting

DTP code	ICD 10 code	ICD10 code description
901S	C84.0	Mycosis fungoides
	C84.1	Sézary syndrome
	C86.6	Lymphomatoid papulosis
	C84.6	Primary cutaneous anaplastic large cell lymphoma
	C86.3	Subcutaneous panniculitis-like T-cell lymphoma
	C84.4	Primary cutaneous gamma delta T-cell lymphoma
	C84.5	Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma
	C86.6	Primary cutaneous acral CD8-positive T-cell lymphoma
	C86.6	Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder

3. Epidemiology

3.1. Primary cutaneous lymphomas (PCL) are classified as non-Hodgkin lymphomas that present in the skin with no evidence of extracutaneous disease at the time of diagnosis (Willemze et al, 2018).
3.2. Within cutaneous lymphomas, there are two types namely, cutaneous T-cell lymphoma (CTCL) and cutaneous B-cell lymphoma (CBCL), depending on the effect on T-cells or B-cells respectively.
3.3. Cutaneous T-cell lymphomas (CTCL) comprise 2% of all non-Hodgkin lymphoma diagnoses in the United States (US) (Ulrickson et al., 2013).

3.4. The most common subtypes are Mycosis Fungoides (MF) and its leukemic presentation, Sézary Syndrome (SS)(Prince, Whittaker and Hoppe, 2009).
3.5. CTCL is the most common type of cutaneous lymphoma constituting approximately 70 – 80% whilst CBCL constitutes 15 - 20% of all PCLs (Sokołowska-wojdyło et al., 2015).
3.6. There are no recent studies that estimate the prevalence of CTCL or MF in sub-Saharan Africa. The latest National Cancer Registry data in South Africa data does not provide any information specifically on the incidence of Mycosis Fungoides and Sézary Syndrome. It is possible that these conditions are reported under non-Hodgkin lymphoma (NICD, 2017)
3.7. The risk factors for CTCL include (Sokołowska-wojdyło et al., 2015):

- Body mass index equal to or larger than 30 kg/m^2
- Cigarette smoking for 40 years or more
- Eczema
- Family history of multiple myeloma
- Professions, such as crop and vegetable farmers, painters, woodworkers and carpenters

4. Classification, staging and risk assessment.

4.1. The PCLs are classified by the WHO as shown in table 2 below.

Table 2 : WHO-EORTC classification for PCL (Willemse, 2018)

Cutaneous T cell lymphoma
Mycosis fungoides (MF) Variants of MF • Folliculotropic MF • Pagetoid reticulosis • Granulomatous slack skin
Sézary syndrome (SS)
Primary cutaneous CD30+ lymphoproliferative disorders • Primary cutaneous anaplastic large cell lymphoma • Lymphomatoid papulosis
Subcutaneous panniculitis-like T cell lymphoma
Extranodal NK/T cell lymphoma, nasal-type
Primary cutaneous peripheral T cell lymphoma-not otherwise specified • Primary cutaneous c/d T cell lymphoma • Primary cutaneous CD8þ aggressive epidermotropic cytotoxic T cell lymphoma

• Primary cutaneous acral CD8þ T cell lymphoma • Primary cutaneous CD4þ small/medium T cell lymphoproliferative disorders
Cutaneous B cell lymphoma
Primary cutaneous marginal zone lymphoma Primary cutaneous follicle centre lymphoma Primary cutaneous diffuse large B cell lymphoma, leg type

4.2. Adequate staging should be carried out to exclude the presence of extracutaneous disease. The prognosis depends on the stage of the disease and clinical staging of MF and SS, which is detailed in table 3 and 4 below.

Table 3: Revised TNMB classification of MF/SS [Reproduced from NCCN 2021 guidelines].

TNMB		**TNMB Classification and Staging of Mycosis fungoides and Sezary Syndrome**
Skin	**T1**	Limited patches[o], papules, and or plaques[p] covering < 10 % of the skin surface
	T2	Patches, papules, and/or plaques covering ≥ 10 % of the skin surface
	T2a	Patch only
	T2b	Plaque ± patch
	T3	One or more tumours[q] (≥ 1 cm in diameter)
	T4	Confluence of erythema ≥ 80 % body surface area
Node	**N0**	No abnormal lymph nodes; biopsy not required
	N1	Abnormal lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2
	N2	Abnormal lymph nodes; histopathology Dutch Gr 2 or NCI LN 3
	N3	Abnormal lymph nodes; histopathology Dutch Gr 3-4 or NCI LN 4
	NX	Abnormal lymph nodes; no histologic confirmation
Visceral	**M0**	No visceral involvement
	M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
	MX	Abnormal visceral site; no histologic confirmation
Blood	**BO**	Absence of significant blood involvement: ≤ 5 % peripheral blood lymphocytes or < 250/ mcL are atypical (Sezary) cells or < 15 % CD4+ /CD26- or CD4+/ CD7- cells of total lymphocytes
	B1	Low blood tumour burden: > 5 % of peripheral blood lymphocytes are atypical (Sezary) cells or ≥ 15 % CD4+CD26- or CD4+CD7- of total lymphocytes but do not meet criteria of B0 or B2
	B2	High blood tumour burden: ≥ 1000/ mcL Sezary cells[n] determined by cytopathology or ≥ 1000 CD4+CD26- or CD4+CD7- cells/µL or other abnormal subset of T lymphocytes by flow cytometry with clone in blood same as that in skin. Other criteria for documenting high blood tumour burden in CD4+ MF / SS include CD4+/CD7- cells ≥ 40 % and CD4+CD26- cells ≥ 30 %.
Lymph Node Classification in MF and SS		
NCI-VA Lymph Node Classification		
LN0	No atypical lymphocytes	
LN1	Occasional and isolated atypical lymphocytes (not arranged in clusters)	

LN2	Many atypical lymphocytes or in 3-6 cell clusters
LN3	Aggregates of atypical lymphocytes; nodal architecture preserved
LN4	Partial / complete effacement of nodal architecture by atypical lymphocytes or frankly neoplastic cells

Dutch criteria for Lymph Nodes

Grade 1	Dermatopathic lymphadenopathy
Grade 2	Early involvement by mycosis fungoides (presence of cerebriform nuclei ≥ 7.5 micrometres
Grade 3	Partial effacement of lymph node architecture; many atypical cerebriform mononuclei cells
Grade 4	Complete effacement of the lymph node architecture

[n] Sezary syndrome is defined by B2 blood involvement and a clonal rearrangement of T-cell antigen receptor (TCR) in the blood (clones should be relevant to clone in the skin)

[o] patch = any size skin lesion without significant elevation or induration. Presence or absence of hypo- or hyperpigmentation, scale, crusting, and /or poikiloderma should be noted.

[p] Plaque = any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or poikiloderma should be noted. Histologic features such as folliculotropism or large cell transformation (LCT) (≥ 25 % large cells), CD30+ OR CD30 -, and clinical features such as ulceration are important to document.

[q] Tumour = at least one ≥ 1 cm diameter solid or nodular lesion with evidence of depth and /or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histologic evidence of LCT has occurred. Phenotyping for CD30 is encouraged.

Table 4: Clinical Staging of MF and SS [Reproduced from NCCN 2021 guidelines].

Clinical stage	T (Skin)	N (Node)	M (Visceral)	B (Blood)
IA (limited skin involvement)	T1 (patches, papules, and or plaques covering < 10 % of the body surface area (BSA)	N0	M0	B0 or B1
IB (Skin only disease)	T2 (Patches, papules, and/or plaques covering ≥ 10 % BSA)	N0	M0	B0 or B1
IIA	T1-2	N1-2	MO	B0 or B1
IIB (Tumour stage disease)	T3 (One or more tumours [≥ 1 cm in diameter])	N0-2	M0	B0 or B1
IIIA (Erythrodermic disease)	T4 (Confluence of erythema ≥ 80 % of BSA)	N0-2	M0	B0
IIIB	T4 (Confluence of erythema ≥ 80 % of BSA)	N0-2	M0	B1

(Erythrodermic disease)				
IVA_1 (Sezary syndrome)	T1-4	N0-2	M0	B2
IVA_2 (Sezary syndrome or non-Sezary)	T1-4	N3	M0	B0 or B1 or B2
IVB (Visceral disease)	T1-4	N0-3	M1	B0 or B1 or B2

5. Recommended work-up for CTCL

5.1. Consultations

5.1.1. PCLs are rare diseases and patients should ideally be seen by a multidisciplinary team which consists of dermatologists, pathologists, haematologists and radiation oncologists. Meticulous diagnosis and precise classification are essential to guide treatment options.

5.1.2. Follow-up should be individualized, depending on the patient: the frequency of follow-up visits varies, depending on the type and stage of disease - every 6 or 12 months in patients with indolent types and stable disease or patients in complete response (CR), to every 4–6 weeks in patients with active or progressive disease.

5.1.3. Follow-up visits should focus on history and physical examination, with additional testing, only if required. Routine imaging after treatment is not required, since tumour responses are visible to the naked eye and, in most instances, recurrences are also localized in the skin.

5.2. Pathology tests

The following baseline tests are PMB level of care for the initial workup:

- Full blood count (FBC) & differential
- Urea and Electrolytes (U&E)
- Full Liver Function Tests (LFT)
- International Normalized Ratio (INR) & Partial Thromboplastin Time (PTT)
- Lactate dehydrogenase (LDH)
- Calcium, magnesium, phosphate
- Haemolytic screen: Coombs, haptoglobin, unconjugated bilirubin, reticulocytes.
- Immunoglobulins
- Hepatitis BsAg/core antibody
- Hepatitis C serology
- Baseline haematinics – iron studies, folate, Vitamin B12

- Glucose
- Uric acid
- Beta-2 microglobulin
- HTLV-1, where indicated
- Epstein-Barr virus (EBV)
- Human immunodeficiency virus (HIV)
- Pregnancy test in women of child-bearing age

5.3. **Histopathology**

5.3.1. Dermatopathology forms the basis for the diagnosis of the primary cutaneous lymphomas, which may sometimes be diagnosed from a lymph node specimen or a biopsy specimen from another in-filtrated organ (Sokołowska-wojdyło et al., 2015; Willemze et al., 2018).

5.3.2. The following are PMB level of care:

- Histology (tissue biopsy) – Immunohistochemistry (IHC); morphology. Multiple biopsies may be needed particularly for MF, which can have a slow evolution and may be difficult to diagnose in the early stages.
- Bone marrow aspirate and trephine biopsy
- Cytogenetics
- FISH studies (where appropriate should be used as an adjunct to cytogenetics studies)
- Peripheral blood and bone marrow flow cytometry –to exclude Sézary syndrome.
- Lymph node biopsy – immunohistochemistry, TCR gene rearrangement.

5.4. **Radiology**

5.4.1. Although CTCLs primarily develop in the skin, at times they progress to involve the lymph nodes, blood, and visceral organs. Imaging aids in the evaluation of lymphadenopathy and/or presence of organomegaly (Sundar et al., 2021).

5.4.2. Patients with unfavourable features (T2 or higher, folliculotropic MS or large cell transformation, palpable adenopathy, or abnormal laboratory studies) should undergo either a CT or PET-CT scan of the chest, abdomen and pelvis (Sundar et al., 2021).

5.4.3. CT scans of the chest, abdomen and pelvis alone or with FDG-PET (Fluorodeoxyglucose-positron emission tomography) (optional in patients with early-stage MF) is PMB level of care.

5.4.4. Integrated PET-CT was found to be more sensitive for detection of lymph node involvement than CT alone (D'Souza et al., 2013). PET-CT scan is PMB level of care on motivation as it is preferred in patients with extranodal disease not adequately imaged by CT.

6. Management of CTCL

6.1. Selection of therapy is based on the clinical and pathologic features. Early stage disease with limited skin involvement (stage IA or stage IB – IIA) is usually treated by a dermatologist in collaboration with a radiation oncologist using skin-directed therapies that can provide disease control without major cumulative toxicities. (Sundar et al., 2021)

6.2. Topical therapy, phototherapy, radiation therapy, and total skin electronic beam therapy (TSEBT) is PMB level of care and shown in table 6 below.

Topical therapy

6.3. In the PROCLIPI study, in which a total of 395 newly diagnosed patients with early-stage MF (stage IA-IIA) were recruited from 41 centres in 17 countries, a prospective analysis was done to identify (i) differences in first-line approaches according to tumour-nodes-metastasis-blood (TNMB) staging; (ii) parameters related to a first-line systemic approach and (iii) response rates and QoL measures (Quaglino et al., 2020).

6.4. Skin directed therapy was found to be superior to systemic therapy even in patients with higher clinical stage, presence of plaques and, folliculotropic mycosis fungoides (FMF). The overall response rate (ORR) to first-line skin directed therapy was 73% compared to 57% for systemic therapy (Quaglino et al., 2020).

6.5. Topical corticosteroids are effective for early-stage MF (especially patch-stage MF). They result in measurable improvement in BSA involvement and high ORR (94%; 63% complete response (CR); 13% partial response (PR) and 82% (25% CR; 57 PR), respectively in patients with stage T1 and T2 disease. The downfall is skin atrophy or striae formation with long term use (Sundar et al., 2021).

6.6. The use of topical mechlorethamine for patients with MF resulted in an ORR of 83% (50% CR). Patients with T1 disease had a higher ORR (93% vs. 72%), CR rate (65% vs. 34%), longer median OS (21 months vs. 15 months), and higher 5-year OS rate (97% vs. 72%) than those with T2 disease (Kim et al., 2003).

6.7. In a phase I-II trial of 67 patients with early-stage MF, topical retinoids resulted in ORR of 63% (21% CR) and the estimated response duration was 99 weeks. The response rates were higher among the patients who had no prior therapy compared to those who had received prior topical therapies (75% vs. 67%) (Breneman et al., 2002). In a phase III multicentre study of 50 patients with early-stage refractory MF, the ORR was 44% (8% CR) (Heald et al., 2003).

6.8. Skin directed therapy with retinoids is PMB level of care.

Systemic therapy

6.9. Systemic disease / advanced-stage disease (≥ stage IIB) requires addition of chemotherapy which is often combined with skin-directed therapy. Stage IIB patients with single or few T3 lesions can be treated with external beam RT with further delay of systemic therapy, and TSEBT may be used with stage IB -IIB disease with excellent response (Sundar et al., 2021).

6.10. Systematic therapy can be considered for stage IB-IIA disease with higher skin disease burden, concerning pathologic features, predominant plaque disease, and/or inadequate response to skin-directed therapy (Sundar et al., 2021).

6.11. In a phase III randomised study (ALCANZA), brentuximab vedotin resulted in superior clinical outcomes compared to methotrexate or bexarotene in patients with previously treated CD30-expressing MF. At a median follow-up of 23 months, the primary endpoint, ORR lasting for ≥ 4 months was significantly higher for brentuximab vedotin compared to methotrexate or bexarotene in the intention-to-treat population (56% [16%CR] VS. 13% [2% CR]; $P < 0.0001$) (Prince et al., 2017). Although brentuximab vedotin has shown good outcomes, it is not currently PMB level of care and funding is at the discretion of the scheme.

6.12. Alemtuzumab has shown significant clinical activity in patients with previously treated advanced SS and MF. Alemtuzumab is not currently PMB level of care and funding is at the discretion of the scheme.

6.13. Gemcitabine and liposomal doxorubicin have also shown substantial activity in patients with advanced MF and SS (Sundar et al, 2021). Gemcitabine and doxorubicin are PMB level of care. The pegylated liposomal formulation of doxorubicin is reimbursed at the discretion of the scheme.

Radiation therapy

6.14. Radiation therapy is effective in MF and patients with unilesional or stage IA MF may be managed with local RT alone, resulting in an ORR of 97% to 100%. Low-dose involved -field (IFRT) have been shown to result in high response rates without any toxicity in patients with MF (Piccinno et al., 2014; Specht et al., 2015).

Stem cell transplant

6.15. Allogeneic haematopoietic cell transplant (HCT) has a role in a subset of patients with advanced-stage MF and SS who have received multiple lines of therapy. In a multicentre retrospective analysis of 37 patients with advanced-stage primary CTCL treated with allogeneic HCT (24 patients had stage IV MF and SS or disseminated nodal or visceral involvement), after a median follow-up of 29 months, the incidence of relapse was 56% and the estimated 2-year OS and PFS rates were 57% and 31%, respectively (de Masson et al., 2014). In a retrospective analysis of patients with advanced-stage MF and SS in European Group for Blood and Marrow Transplantation (EBMT) database (n = 60) treated with allogeneic HCT, the 5-year PFS and OS rates were 32% and 46%, respectively. The corresponding 7-year survival rates were 44% and 30%, respectively (Duarte et al., 2014). Allogeneic stem cell transplantation is used for selected patients and PMB level of care when clinically appropriate.

6.16. Given the poor efficacy results of autologous stem cell transplant (Willemze et al, 2018), this is not recommended as PMB level of care for both MF and SS.

Extracorporeal photophoresis (ECP)

6.17. ECP therapy in which patient's leukocytes are removed by leukapheresis, treated extracorporeally with 8-methoxypsoralen and UVA, and then returned to the patient (McGirt et al., 2010; Quaglino et al., 2013; Knobler et al., 2020).

6.18. ECP may be an appropriate systemic therapy for patients with some level of blood involvement (B1 or B2). In a retrospective evaluation of 50 MF patients who received ECP for clinical activity, toxicity, and response and outcome rates, it was found that combined treatment with ECP significantly improved the OS (84 months vs 62 months, P=0.005), and had a low frequency of side effects (Atilla et al., 2017).

Table 6: Summary of treatment options for MF and SS recommended as PMB level of care

Condition	Clinical stage	Recommended treatment
Mycosis Fungoides (MF)	**Stage IA – IIA**	• Topical steroids • Narrow band Ultraviolet B • Psoralens plus ultraviolet A (PUVA) • Topical mechlorethamine • Local RT • Skin directed therapies with retinoids • Total skin electron beam therapy (TSEBT) – available in state
	Stage IIB	• Skin directed therapy and local RT • Skin directed therapy and retinoids • TSEBT • Gemcitabine monotherapy • Allogeneic haematopoietic stem cell transplant
	Stage III	• Skin directed therapies with Retinoids

		• Extracorporeal photopheresis with/ without Retinoids • Methotrexate • Total skin electron beam therapy
	Stage IV	• Cyclophosphamide • Vincristine • Prednisone • Gemcitabine • Doxorubicin • Allogeneic haematopoietic stem cell transplant
Sézary Syndrome (SS)		• Extracorporeal photophoresis with/ without Retinoids • PUVA • Prednisone with chlorambucil • Methotrexate • Gemcitabine • Doxorubicin • Allogeneic haematopoietic stem cell transplant

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