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F.2 Pegylated liposomal doxorubicine - 2mg/mL in 10 mL vial and 2 mg/mL in 50 mL vial.

MSF strongly supports the inclusion of pegylated liposomal doxorubicin in the Complementary List of Section 8.2.1 "Cytotoxic medicines" in both the WHO Model List of Essential Medicines (EML) and the WHO Model List of Essential Medicines for Children (EMLc), for treatment of Kaposi's sarcoma, in adults, adolescents, and children.
Kaposi's sarcoma (KS) is a multifocal neoplasm of lymphatic endothelium-derived cells infected with human herpesvirus 8. Four clinical subtypes are distinguished: the classic, the endemic, the epidemic subtype in HIV positive (HIV-KS) patients and the iatrogenic subtype.
HIV-KS is associated with cutaneous and oral lesions, then with visceral lesions in advanced disease (gastrointestinal tract and lungs). Many cases of HIV-KS can be managed with antiretroviral therapy alone, but advanced stage requires chemotherapy. The application highlights that 82% of KS occurs in low- and middle-income countries (LMICs), 64% occurs in the WHO AFRO region and a disproportionately large proportion (85%) of deaths from KS occurs in Africa. In resource-poor settings, local treatments (radiotherapy, intralesional chemotherapy) may be difficult to access, thus access to chemotherapy is important.

Pegylated liposomal doxorubicin (PLD) is a cytotoxic chemotherapy indicated in the treatment of Kaposi's sarcoma, in adults, adolescents, and children with severe disease, and in patients with non-severe disease, where it is symptomatic or cosmetically unacceptable.

Since 2015, paclitaxel, vincristine, vinblastine, bleomycin and doxorubicin (non liposomal) are listed in the EMLs for treatment of Kaposi's sarcoma, following the decision of the Expert Committee recommending that, on the basis of the evidence presented, these medicines, already listed on the Complementary List, be specifically endorsed for the treatment of Kaposi sarcoma. The Expert Committee stated that "no studies supported the superiority of liposomal daunorubicin and pegylated liposomal doxorubicin when compared to non-liposomal doxorubicin with bleomycin and vincristine or vinblastine (ABV). Moreover, they are more costly and, without clear, proved incremental benefit over other regimens, they are not proposed for inclusion in the EML"[1]. Since the meeting of the 2015 Expert Committee, additional clinical evidence has been published, and new lower-cost sources for PLD have become available.

[1] The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2015 (WHO Technical Report Series, No. 994; http://apps.who.int/iris/bitstream/10665/189763/1/9789241209946_eng.pdf.

The 2014 WHO "Guidelines on the treatment of skin and oral HIV-associated conditions in children and adults" recommends immediate antiretroviral therapy (ART) initiation in HIV-infected adults, adolescents and children diagnosed with mild/moderate KS and immediate ART initiation in combination with systemic chemotherapy in HIV-infected adults, adolescents and children diagnosed with severe symptomatic KS. Recommended chemotherapy regimens in adults, adolescents and children may include ABV, BV, and when available or feasible, liposomal anthracyclines (doxorubicin or daunorubicin), paclitaxel or oral etoposide at sites with the infrastructure, staff and resources to administer chemotherapy drugs and provide appropriate monitoring and supportive care.
Chemotherapy can also be considered if KS is progressive despite ART[2].

Currently, most patients in sub-Saharan Africa are treated with bleomycin and vincristine. Of note, older regimens – bleomycin with vincristine or vinblastine (BV) or non-liposomal doxorubicin with bleomycin with vincristine or vinblastine (ABV) are no longer recommended in American nor European guidelines.

After a comprehensive review of the available evidence, the authors of the application concluded that PLD is superior to both BV and ABV, superior to liposomal daunorubicin, non-inferior to paclitaxel and may have a favourable toxicity profile compared to paclitaxel and ABV. PLD as a monotherapy allows to decrease or avoid specific toxicities due to bleomycin (e.g. pulmonary fibrosis) and vincristine (e.g. neuropathy). PLD is recommended as first-line chemotherapy in high-income country guidelines, with paclitaxel as second choice.

In 2019, the European consensus guidelines stated that systemic treatments are reserved for locally aggressive, extensive and disseminated KS: the recommended first-line agents are PLD and paclitaxel. Of note, in HIV-KS; standard first-line therapy is PLD, and second-line therapy are taxanes (such as paclitaxel)[3].
In 2023, as first-line systemic therapy option, the US-based National Comprehensive Cancer Network guidelines recommend PLD as preferred regimen while paclitaxel is the other recommended regimen[4].

MSF performed a prospective, single-arm, open-label observational study in Mozambique to demonstrate the feasibility, safety, and outcomes of treatment with PLD in patients HIV-KS in a low-resource setting. The traditional regimen in Mozambique includes conventional doxorubicin, bleomycin and vincristine, which is poorly tolerated. In 2016, PLD was introduced at a specialized outpatient center in Maputo, Mozambique. The study showed that PLD had an overall response rate of 80% and that the response with PLD was achieved more quickly and with less side-effects than they

[2] Guidelines on the treatment of skin and oral HIV-associated conditions in children and adults. WHO, 2014. https://www.who.int/publications/i/item/9789241548915
[3] Lebbe C, Garbe C, Stratigos AJ et al; European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organisation for Research and Treatment of Cancer (EORTC). Diagnosis and treatment of Kaposi's sarcoma: European consensus-based interdisciplinary guideline (EDF/EADO/EORTC). Eur J Cancer. 2019 Jun;114:117-127
[4] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Kaposi Sarcoma. Version 1.2022.

had observed with ABV in the same clinical centres in an earlier study. PLD was safe, well-tolerated and effective as first-line treatment of KS in Mozambique[5].

Pharmacokinetics explain the benefits of PLD versus ABV: doxorubicin is encapsulated within pegylated liposomes, which preferentially distribute into tumours due to the greater permeability of the vasculature in KS tumours compared to that in healthy tissue. The concentration of doxorubicin when using PLD is higher within tumours compared to non-liposomal doxorubicin.

MSF would like to draw the attention of the Expert Committee to the following points:

- MSF has been using PLD as their preferred treatment for KS for the last decade with positive operational experience
- Having PLD and paclitaxel as two alternatives for supply would improve access for the treatment of KS patients.
- PLD has been available from the Global Fund Pooled Procurement Mechanism since around 2020.
- The inclusion of PLD in the EMLs will serve as a basis for National Essential Medicines lists and therefore will attract additional manufacturers, will facilitate importations, alert manufacturers about the need for local registrations, allow for better competition between manufacturers in order to further reduce price, increase supply security and improve accessibility, particularly in LMICs.

In light of all these elements, MSF urges the 24th Expert Committee on the Selection and Use of Essential Medicines to include pegylated liposomal doxorubicin in the Complementary List of Section 8.2.1 “Cytotoxic medicines” in both the WHO Model List of Essential Medicines and the WHO Model List of Essential Medicines for Children, for treatment of Kaposi’s sarcoma, in adults, adolescents, and children.

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[5] Coldiron ME, Gutierrez Zamudio AG, Manuel R et al. Outcomes of AIDS-associated Kaposi sarcoma in Mozambique after treatment with pegylated liposomal doxorubicin. Infect Agents Cancer. 2021 Dec;16(1):2. https://epicentre.msf.org/en/publications/outcomes-aids-associated-kaposi-sarcoma-mozambique-after-treatment-pegylated-liposomal