



# **Submissions to the 2023 WHO EML: MSF comments from the humanitarian context**

**24<sup>th</sup> WHO Expert Committee on the Selection and Use of Essential Medicines**  
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# EML: which lens?

- The EML is a **key tool for Primary Health Care**
- The EML must be **inclusive** for the treatment of most vulnerable populations in humanitarian crises and low resource settings
  - medicines should be **available, affordable** and **quality assured**
  - **EML should align with WHO Departmental Guidance**
- Populations in humanitarian contexts and low resource settings have many of the same morbidities as people in high resource settings, yet poor access to the associated EML listed medicines
- Adapted formulations may benefit people in low resource settings to a greater extent, yet are more often unavailable
- Some essential medicines are stockpiled in HICs, while less available in countries with immediate need (e.g. Ebola therapeutics)

# Humanitarian contexts and essential medicines

Recommended characteristics for essential medicines in humanitarian contexts:

- **Affordability and availability**
- **Quality of essential medicines** in “major producing” and “primarily importing” countries
- **Adapted formulations**
  - FDCs / SPCs
  - breakable and dispersible tablets, granules, or pellets rather than syrups for paediatric medicines (amoxicillin/clavulanic acid dispersible tablets)
  - single dose treatments and long-acting formulations (paliperidone 3-month long acting)
  - thermostable rather than cold-chain; longer shelf-lives; easier transportation and storage (amoxicillin/clavulanic acid dispersible tablets versus oral solution)
  - self-administration with pen devices (insulins)
  - oral formulations rather than injectable formulations (deferiprone)
- **Improved safety profiles** in settings where pharmacovigilance and monitoring are challenging (acamprosate versus naltrexone)
- **Importation mechanisms that reduce lead time:** access to narcotics and controlled medicines are currently an urgent issue for some LICs (levetiracetam versus phenobarbital for epilepsy, oral transmucosal fentanyl for pain)

# MSF perspective on submissions of significant impact for humanitarian settings

## ❑ **Children: Medicines for mental health in EMLc**

- ❑ **Need for a comprehensive review of antipsychotic medicines for children;** MSF recommends to retain haloperidol and add risperidone for the treatment of psychosis and recommends evaluating other antipsychotics (aripiprazole, olanzapine, quetiapine)
- ❑ MSF recommends to retain fluoxetine for the treatment of moderate-to-severe depressive disorders

## ❑ **NCDs: CVD and diabetes**

- ❑ **FDCs of cardiovascular medicines:** MSF supports, while noting the application with the proposed combinations and doses remains complex and simplified algorithms as part of a public health approach for the implementation of FDC for primary and secondary prevention are needed
- ❑ **Insulin pen devices:** MSF welcomes the ongoing focus to improve access to insulin for people globally, including overcoming the ongoing double standard of both access and adapted delivery devices to improve patient care
- ❑ **GLP-1 Agonists for obesity:** As this class is also efficient for diabetes management, if it is included "only" for obesity, countries will not have flexibility to consider it for people with diabetes, where it may make a significant impact on their diabetes management. Once weekly injectable GLP-1 agonist does not require regular self-blood glucose monitoring, could provide a more acceptable and effective add-on therapy, particularly in challenging humanitarian and low-resource settings.

- ❑ **RUTF:** MSF supports the inclusion, on the condition that it will be included in the new distinct category mentioned in the application, using the codex terminology for its name, and with an acknowledgment that Codex Alimentarius standards and guidelines apply for their manufacturing

# Affordability and availability of QA'd sources of medications

- **Chemotherapy: pegylated liposomal doxorubicin**

MSF recommended treatment for Kaposi's sarcoma for the last decade with positive operational experience (favourable safety, tolerability and efficacy profile)

- **Antibiotics:**

- **Registration to aid availability and procurement gaps:**

- most carbapenems are not registered or available in many LMICs
- only half of new antibiotics entering the market between 1999 and 2014 were registered in more than ten countries
- companies often do not file for or withdraw registration due to the costs

- **Tedizolid, imipenem/cilastatin/ relebactam, ceftolozane/tazobactam:**

- currently, access is impossible in most resource limited settings due to prohibitive prices and lack of registration
- actions to foster access are sorely needed given very high prices and limited number of countries where these antibiotics are registered.

# Anti-Ebola mAbs: critical access issue

## MSF recommends:

- expanding the current approach of immediate administration of either mAb114 or REGN-EB3 to include not only neonates under 7 days born to positive mothers, but also individuals who exhibit clinical symptoms and contact history strongly suggestive of Ebola virus infection or who test positive on rapid diagnostic tests (RDT) while awaiting PCR test results
- extending the use of mAbs for post-exposure prophylaxis beyond neonates under 7 days born to positive mothers, to also include presumptive treatment for other high-risk contacts

## These mAbs:

- are not registered in endemic countries
- are registered and stockpiled (at exorbitant price) in a non-endemic HIC

Lack of planning for registration and supply based upon burden of disease; lack of transparency around price, supply capacity, and access conditions from manufacturers

April 21<sup>st</sup>, 2023

**MSF Statement: 24<sup>th</sup> Expert Committee, WHO Model List of Essential Medicines (EML) including Essential Medicines for Children (EMLc)**

In this statement, MSF would like to share some more general comments on the EML and highlight some key points of the detailed comments provided for the Expert Committee discussion.

**General comments:**

MSF would like to emphasize the following points:

- Medicines should be quality-assured according to internationally agreed standards, manufactured under good manufacturing practice (GMP) regulations to assure that quality is built into the design and manufacturing process at every step and distributed according to good distribution practice (GDP) regulations.
- Moreover, medicines should be affordable for low- and middle-income countries (LMICs).
- Alignment between the EML and the prequalification scope continues to be very important and should be ensured. This collaboration helps improve availability of quality-assured medicines.
- EML applications should provide all existing randomized controlled trials (RCTs), pharmacokinetic studies, as well as data on tolerability, availability, affordability, cost-effectiveness.

**Paediatric dosage forms:**

Paediatric formulations are needed to increase ease, safety of administration and adherence to treatment. Paediatric dosage forms like dispersible tablets easily dissolved in liquids or soft food, oral powder, oral granules, oral pellets should be promoted and should reach internationally agreed quality standards.

**Key points of the MSF detailed comments:**

**1 - MSF warmly welcomes the addition of Anti-Ebola monoclonal antibodies and oral transmucosal fentanyl citrate but would like to request extended indications:**

- **Anti-Ebola virus disease monoclonal antibodies**

Based on the available evidence regarding the efficacy of monoclonal antibodies (mAbs) against Ebola virus and their optimal use in the early stages of the disease demonstrated in the PALM trial, MSF recommends a less restrictive approach towards their administration. Considering the severe and often fatal nature of Ebola virus disease, mAb114 and REGN-

EB3 should be more widely utilized. Regarding mAbs as treatment, MSF recommends expanding the current approach of immediate administration of either mAb114 or REGN-EB3 to include not only neonates under 7 days born to positive mothers, but also individuals who exhibit clinical symptoms and contact history strongly suggestive of Ebola virus infection or who test positive on rapid diagnostic tests while awaiting PCR test results. Regarding mAbs as post-exposure prophylaxis: MSF recommends extending the use of mAbs for post-exposure prophylaxis beyond neonates under 7 days born to positive mothers, to also include presumptive treatment for other high-risk contacts. Scientific evaluation on this indication has been hindered by the lack of access to the therapeutics, however, both animal studies and established medical knowledge along with experience with emergency use during outbreaks provide compelling evidence of its safety and efficacy. Furthermore, prior vaccination with rVSV-EBOV seems to have a synergetic effect with mAbs given post-exposure.

- **Fentanyl citrate, oral transmucosal (OTFC)**

The application reserves OTFC to treatment of breakthrough pain in opioid-dependant cancer patients. It has been estimated that 5.5 billion people live in countries with little or no access to opioids; upward of 80% of the world's population lacking access to basic pain relief. Paradoxically, those 80% are mostly in poorer countries, and their need for pain relief is heightened by a relative absence of curative care such as surgery, or treatment for both communicable and noncommunicable diseases causing pain. OTFC is a rapid and non-invasive pain management strategy that has considerable implications for use in hospital, prehospital and austere environments. Despite the fact that opioids have been recognised as absolutely necessary for medical purposes (morphine is included in the EML since 1977), MSF and other organizations struggle to maintain an access to opioids particularly morphine, with often little to no alternatives. Considering existing barriers to access to pain management treatment in LMICs, MSF recommends that OTFC formulations should be added to the EML with expanded indications to include acute and trauma pain both in hospital and prehospital settings in opioid naïve patients.

## 2 - MSF supports all the following inclusions:

- **Pretomanid** for multidrug-resistant or rifampicin-resistant tuberculosis: MSF has been using pretomanid in its programs since 2022. Currently, pretomanid is used in MSF programs in Belarus, Uzbekistan, Sierra Leone, Pakistan and Tajikistan.
- **Ceftolozane/tazobactam**: MSF supports this inclusion if it is included as a Reserve antibiotic indicated only for the treatment of DTR-*P.aeruginosa*. MSF **does not support** ceftolozane/tazobactam for treatment of ESBL/ceftriaxone-R Enterobacterales or for treatment of *P.aeruginosa* still susceptible to other beta lactams or fluoroquinolones.
- **Imipenem/cilastatin/relebactam**: MSF supports this inclusion if it is included as a Reserve antibiotic and should be used solely for the treatment of for DTR-*P.aeruginosa* and CRE (KPC-producers) when there are no other antibiotic alternatives. MSF **does not support**



imipenem/cilastatin/relebactam indication for less extensive forms of resistance for which there are safe and effective alternatives, e.g. for treatment of Enterobacterales ESBL producers still susceptible to carbapenems.

- **Tedizolid:** MSF highlights that oral options with high bioavailability and favourable side effect/interaction profiles are lacking. MSF notices that data regarding efficacy and tolerability for use in the treatment of osteomyelitis are insufficient. Alternative to linezolid (or rifampicin) for treatment of MDR gram positives pathogens for osteomyelitis is urgently needed.

MSF would like to highlight that currently, access to ceftolozane/tazobactam, imipenem/cilastatin/relebactam and tedizolid is impossible in most resource limited settings due to prohibitive prices and lack of registration, barriers which should be worked on to guarantee that all patients in need can benefit (together with microbiology laboratory support for diagnosis). MSF emphasized that actions to foster access are sorely needed given very high prices and limited number of countries where these antibiotics are registered.

- **COVID-19 medicines** (baricitinib, molnupiravir, nirmatrelvir/ritonavir, remdesivir, tocilizumab). MSF would like to highlight the access issues for some COVID-19 medicines.
  - Baricitinib: Currently, this medicine is provided commercially by its producer, which has been granted patents in over 50 countries. Baricitinib is not part of the Medicines Patent Pool initiative, and is not being currently procured through the ACT Accelerator programme. Baricitinib is already approved for other indications such as rheumatoid arthritis, and generic versions are already available in India and Bangladesh at much lower prices than those of the patent holder. However, in many countries including in countries hit hard by the pandemic, such as Brazil, Russia, South Africa and Indonesia, generic baricitinib remains unavailable due to patent restrictions.
  - Nirmatrelvir/ritonavir: Currently, nirmatrelvir-ritonavir is provided commercially by the patent holder (Pfizer). In March 2022, the Medicines Patent Pool announced that it has signed agreements with 35 generic manufacturing companies to produce low-cost, generic versions of nirmatrelvir in combination with ritonavir for supply in 95 low- and-middle-income countries. MSF would like to emphasize that the agreements signed between the Medicines Patent Pool and 35 manufacturers to produce and supply nirmatrelvir/ritonavir are a welcome step, but the signed agreement only covers 53 percent of the world's population and excludes millions of people in middle-income countries. Most Latin American countries, including Brazil, are left out of this deal, as well as other middle-income countries, such as China, Malaysia and Thailand – this will have a chilling effect on the availability of more affordable generic versions of the drug produced under this license if Pfizer is granted patents in those countries.
  - Tocilizumab: Currently, tocilizumab is provided commercially by the patent holder, which has committed up to 250,000 doses through the ACT-Accelerator Transition Plan. Three generics have been already WHO prequalified. Sarilumab is currently under patent. Tocilizumab and sarilumab are not part of the Medicines Patent Pool initiative. MSF

would like to highlight that even though tocilizumab has been on the market since 2009 for treatment of rheumatologic diseases, access has remained a challenge. As most of the existing monoclonal antibodies, tocilizumab has been priced extremely high, and are hence virtually impossible to access in low- and middle-income countries. The main patent on tocilizumab expired in 2017, yet several secondary patents remain on the medicine in a number of low- and middle-income countries that may cause uncertainties.

- **Levetiracetam:** For managing epilepsy and status epilepticus, MSF clinical guidelines include phenytoin, phenobarbital, sodium valproate, carbamazepine, and benzodiazepines. Levetiracetam was introduced in MSF programs 5 years ago due to its safety profile for both children and adults. The efficacy of levetiracetam is comparable to older anti-seizure drugs and can be used in a broader range of clinical scenarios than any single older anti-seizure drugs (broader spectrum of use, no cardiac monitoring unlike phenytoin, better safety profile, no monitoring of serum levels to assess for toxicity or subtherapeutic levels unlike valproic acid, less interactions).
- **Sevoflurane:** Currently, there are only two volatile inhalational anaesthetic agents, halothane and isoflurane, included in the EML. Similarly, MSF uses both as standard anaesthetic agents. However, MSF has been actively phasing out halothane in favour of isoflurane over the last decade. Halothane remains used as a second choice wherever supply or delivery systems for isoflurane are absent. Sevoflurane has been introduced in certain programs where appropriate delivery systems are available onsite or can be sourced easily. MSF would like to emphasize the necessity to advocate for a wider availability of means of administration (vaporizers), monitoring (gas analysers) and absorption (scavenging systems).
- **Ready-to-use therapeutic food (RUTF):** MSF notes that UNICEF and the WHO Nutrition and Food Safety (NFS) Department have submitted a proposal to develop an appropriate category for therapeutic foods. This submission addresses MSF's concern regarding the risk of requirements by regulatory bodies of pharmaceutical standards for the manufacturing of RUTF – raised during previous applications for the addition of RUTF to the EMLs (in 2017 and 2019). MSF therefore now supports the inclusion of RUTF in the EMLs, *on the condition that it will be included in the newly created category described above, and with a clear mention that Codex Alimentarius standards and guidelines apply for their manufacturing (not to be confused with pharmaceutical standards)*. MSF recommends consistently use of the terminology defined by Codex – namely either “Food for Special Dietary Use”, to allow inclusion of more products in the future, or the more specific “Food for Special Medical Purpose” – for the new category to be created in the EMLs.
- **Fixed-dose combinations of cardiovascular medicines:** MSF supports the inclusion of FDC formulations, as they will facilitate access and improve rates of control within MSF projects in humanitarian settings, and support scale up within broader ministry of health programmes. Their inclusion remains an important step towards achieving improved global control of cardiovascular disease. In addition, MSF considers the application with the proposed combinations and doses remains complex and simplified algorithms as part of a

public health approach for the implementation of FDC for primary and secondary prevention are needed.

- **Olanzapine:** MSF strongly supports this inclusion for the treatment of psychotic disorders.
- **Quetiapine:** MSF strongly supports this inclusion for bipolar disorders, with a restricted square box including aripiprazole, olanzapine and paliperidone as therapeutic alternatives but MSF would like to highlight that haloperidol and risperidone should also be considered for the treatment of bipolar disorders, following the recommendations from the British Association for Psychopharmacology.
- **New formulation for paliperidone palmitate: 3-month long-acting injection (PP3M).** In low- and -middle income countries, regular clinical follow-up is not easily established and maintained, and the 3-monthly administration of paliperidone palmitate long-acting injection can allow optimal medical care for maintenance treatment. Reduced risk of missing daily intake of pills, increasing individual treatment options, better adherence to treatment and ease of control of drug dosage are the main advantages presenting by long-acting injections. They benefit to patients with limited access to medical care, to homeless and underserved population.
- **New formulation for children: amoxicillin + clavulanic acid dispersible tablets (200mg + 28.5 mg, 7:1 ratio).** This child-friendly formulation will ease administration and improve the tolerance, due to the 7:1 ratio. MSF suggests to include also 8:1 ratio in order to ease supply in all settings and to reserve the 4:1 ratio for multidrug resistant tuberculosis programs only (for use in combination with meropenem or imipenem + cilastatin).
- **New formulation: pegylated liposomal doxorubicin (PLD).** 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-Kaposi's sarcoma in a low resource setting. 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 had observed with non-liposomal doxorubicin with bleomycin with vincristine or vinblastine (ABV) in the same clinical centres in an earlier study. MSF has been using PLD as their preferred treatment for Kaposi's sarcoma for the last decade with positive operational experience. Having PLD and paclitaxel as two alternatives for supply would improve access for the treatment of Kaposi's sarcoma patients.
- **New formulation: ferrous salt + folic acid (60 mg + 2.8 mg) tablet:** In the contexts in which MSF operates, the implementation of this FDC formulation of ferrous salt plus folic acid, for a weekly intake instead a once-daily intake for the currently included ferrous salt (60 mg iron + 400 µg folic acid) will be an important step in reducing anaemia in menstruating women and adolescent girls and reducing the risk of neural tube defect affected pregnancies.

**3 - MSF welcomes** the proposals from the different WHO departments, aligned with the recent recommendations and guidelines, for:

- The removal of age restriction for 2 antituberculosis medicines for children, **bedaquiline** 20 mg scored tablets and **delamanid** 25 mg dispersible tablet.
- The deletion of antituberculosis medicines, dasabuvir, ombitasvir/paritaprevir/ ritonavir and pegylated interferon alfa (2a & 2b) for hepatitis C virus infection according to the existing guidelines.

#### **4 - Comments on Mental Health Medicines for Children: proposal for deletion of chlorpromazine and haloperidol for psychotic disorders and fluoxetine for depressive disorder from EMLc.**

These deletions would entirely suppressed the section 24 “Medicines for mental and behavioural disorders” from the EMLc. Waiting for a comprehensive review of antipsychotics medicines for children, MSF strongly recommends to retain haloperidol and add risperidone on the EMLc, in order to have one antipsychotic drug and an alternative at least for the treatment of psychosis, in particular for the treatment of acute agitation in children. MSF recommends evaluating other antipsychotics (aripiprazole, olanzapine, quetiapine) for the treatment of psychosis in children. Risperidone is already included in the EML since 2013 and applications are submitted for inclusion of olanzapine and quetiapine, for treatment of psychosis in adults. Currently, fluoxetine is the only antidepressant included in the EMLc. Its deletion would imply the absence in EMLc of pharmacological treatment for children with depression. MSF strongly recommends to retain fluoxetine in the EMLc, for the treatment of moderate-to-severe depressive disorder in children. Fluoxetine is the recommended first-line medication for depression and anxiety disorders in children and adolescents by the American Academy of Child and Adolescent Psychiatry (AACAP) and the UK National Institute for Health and Care Excellence (NICE) recommends that when an antidepressant is prescribed to a child, it should be fluoxetine as this is the only antidepressant for which clinical trial evidence shows that the benefits outweigh the risks. A recent met-analysis (including 71 trials, 9510 participants) shows that despite the scarcity of high-quality evidence, fluoxetine (alone or in combination with cognitive behavioural therapy) seems to be the best choice for the acute treatment of moderate-to-severe depressive disorder in children and adolescents. The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have approved fluoxetine for children and adolescents aged 8 years and above.

#### **5 - Comments on diabetes management:**

MSF highlights the importance to raise awareness of the gaps in access to treatment, and to recognize its urgency especially for those living with type 1 diabetes.

- Insulins pen devices:

Currently, in the majority of low- and middle-income settings, when insulin is available, it is still mainly delivered using vials with insulin syringes and needles. This is due to the more prominent inclusion of insulin vials on national EMLs (following WHO’s Model List) and in some settings comparative prices of the different presentations. However, in the majority of high-income settings, vials with insulin syringes and needles are rarely used due to the additional burden placed on people living with diabetes. The lack of cartridges and disposable pens included on the EML therefore continues to underpin this double standard.

MSF would like to emphasize that people living with diabetes reuse syringes and needles with the result of increased risk of infection and pain. MSF has introduced disposable pens in select projects primarily for people living with type 1 diabetes. Operational experience from these programs supports the finding that insulin pens improve the quality of life for children and their caregivers and adult users. Health care workers find that health education messages can be simplified for pens as compared to vials and syringes. Use of pens has also provided improved confidence between healthcare workers and patients to provide accurate dosing and less reluctance to adjust and increase dosing. MSF is currently undertaking a formal qualitative study to assess this in a humanitarian context.

The differential prices of the presentations have to date been the primary reason given for not using these devices more routinely in most low- and middle-income settings. The insulin market remains dominated by three pharmaceutical companies with poor market competition. This application for additional insulin presentations to both the EML and EMLc could encourage biosimilar manufacturers to submit dossiers for WHO prequalification to increase availability and additional market competition, whilst ensuring quality. The inclusion of these insulin presentations would also support advocacy towards insulin manufacturers to include these additional presentations in pricing negotiations offered to low- and middle-income countries.

- Glucagon-like peptide-1 receptor agonists (GLP-1 RAs):

MSF welcomes the consideration of GLP-1 RAs by the Expert Committee for both the indication of diabetes and obesity. Based on current evidence and clear cardiovascular benefits, MSF has incorporated GLP-1 RAs into their 2023 treatment guidelines for type 2 diabetes mellitus (T2DM) and strongly supports this indication. MSF welcomes the consideration of obesity management therapeutics but have concerns if the GLP-1 agonists are not also to be included for the management of people living with diabetes. With both indications listed, countries can then assess priority needs and cost effectiveness, considering the benefit of this class of medicines across populations.

Increasing access to medicines for the management of diabetes requires a multi-factorial approach. This status quo needs to change as today, still only half of those who require insulin have secure access to it.

Thank you for giving us the opportunity to share MSF comments, concerns and suggestions.



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