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A.20 Imipemem/Cilastatin/Relebactam

MSF notices the application for the inclusion of imipenem/cilastatin/relebactam in Section 6.2.3 "Reserve group antibiotics" in the WHO Model List of Essential Medicines (EML).

Imipenem, is a carbapenem antibacterial, cilastatin is a renal dehydropeptidase inhibitor, and relebactam is a beta-lactamase inhibitor that protects imipenem from degradation by certain serine beta-lactamases such as SHV (sulfhydryl variable), TEM (temoneira), CTX-M (cefotaximase-Munich), P99 (*Enterobacter cloacae* P99), PDC (*Pseudomonas*-derived cephalosporinase), and KPC (*Klebsiella pneumoniae* carbapenemase).

Imipenem/cilastatin/relebactam is particularly useful for treatment of difficult-to-treat resistant (DTR) *Pseudomonas aeruginosa (P.aeruginosa)* (carbapenem-resistant/MDR/XDR), while it is also active against carbapenem-resistant Enterobacterales (CRE) KPC-producers.

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

- The published experience with imipenem/cilastatin/relebactam compared to other available antibiotics (eg. ceftazidime/avibactam for both CRE KPC-producers and DTR-*P.aeruginosa* and ceftolozane/tazobactam for DTR-*P.aeruginosa*) is limited.

- Discrepancies emerge between the recent USA guidelines of the Infectious Diseases Society of America (IDSA 2022)[1] which recommends imipenem/cilastatin/relebactam as an alternative agent for CRE (KPC-producers) and DTR-*P.aeruginosa* and the recent European guidelines of the European Society of Clinical Microbiology and Infectious Diseases (ESCMIDD 2022)[2] which refrain from making recommendations given lack of clinical data.

[1] Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America **2022**; Version 1.1. Available at https://www.idsociety.org/practice-guideline/amr-guidance/

[2] Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, de Waele J, Daikos GL, Akova M, Harbarth S, Pulcini C, Garnacho-Montero J, Seme K, Tumbarello M, Lindemann PC, Gandra S, Yu Y, Bassetti M, Mouton JW, Tacconelli E, Rodríguez-Baño J. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). Clin Microbiol Infect. 2022 Apr;28(4):521-547.

- Currently, access 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 imipenem/cilastatin/relebactam is registered.

- The inclusion of imipemem/cilastatin/relebactam in the EML will serve as a basis for National Essential Medicines lists and therefore will motivate additional manufacturers, particularly in low- and middle-income countries.

In light of this elements, MSF urges the 24th Expert Committee on the Selection and Use of Essential Medicines to consider the inclusion of imipenem/cilastatin/relebactam in the WHO Model List of Essential Medicines if it is included in the WHO Model List of Essential Medicines as a Reserve antibiotic (Section 6.2.3 Reserve group antibiotics) 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.

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