M E M O R A N D U M

From:	Director, GCP	**To:**	Director, HPS	**Date: 31 March 2023**
Our ref:		**Attention:**		
Your ref:		**Through:**		
Originator:	AC/hs	**Subject:**	APPLICATIONS TO THE 24 TH EXPERT COMMITTEE ON SELECTION AND USE OF ESSENTIAL MEDICINES, 24 – 28 APRIL 2023	

I would like to thank you for requesting the input of the AMR Global Coordination Department concerning the applications received for the inclusion of certain antibiotics in the 2023 Model List of Essential Medicines (EML) and the Model List of Essential Medicines for Children (EMLc).

Our Department has reviewed the applications and overall, we support the inclusion of ceftazolane + tazobactam (EML and EMLc), imipenem + cilastatin + relebactam (EML), and tedizolid phosphate (EML), for the indications outlined in their respective applications. Should the EML/EMLc committee agree with our recommendation, and in line with the WHO AWaRE classification of antibiotics, we support the classification of the aforementioned medicines in the Reserve Group of antibiotics that should only be used for treatment of confirmed or suspected infections due to multidrug-resistant organisms. We also would like to stress that the use of these medicines must be always informed by evidence-based guidance and strong stewardship activities.

We also support and welcome the addition of the optimized formulation of amoxicillin/clavulanate (7:1 ratio dispersible tablet) to the EMLc, as a therapeutic alternative (to the 4:1 powder for oral suspension) for the same previously proposed indications, as outlined in the application.

We have also had the opportunity to review the application for flomoxef sodium. The medicine has been proposed for addition to the EML and EMLc as a Watch group antibiotic for treatment of mild/moderate intraabdominal infections (IAIs), and upper urinary tract infections (upper UTIs). We first would like to acknowledge that this product could have an added role in the treatment of the indications outlined globally. We also note that this product could potentially be a viable carbapenem-sparing option for the treatment/management of resistant bacterial infections caused by ESBL-PE infections, especially in settings where the prevalence of ESBL-PE is high. However, more in vivo data would be needed to support its inclusion into the 2023 EML/EMLc. Flomoxef sodium could be considered for inclusion in future EML/EMLc once more data become available. Finally, we would like to note that this drug may be of interest for the management of neonatal sepsis, but a decision is likely premature at this stage. New data from planned and ongoing GARDP studies in neonates such as NeoOBS, and NeoSep1, could improve the understanding of the role flomoxef sodium and other antibiotics could play in treatment of neonatal sepsis.

Please find our full response to the proposed applications in the annex to this Memo.

Should you have any questions regarding these comments, please do not hesitate to contact Dr Alexandra Cameron, (camerona@who.int), or Dr Hatim Sati (satihat@who.int), AMR Global Coordination Department.

Finally, I would like to thank you for your continued cooperation.

Dr Haileyesus Getahun

ENCL.: (1)

ENCLOSURE

Re: Applications for updating the 2023 Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc).

In response to your request for input and comments on the applications relevant to the areas of work covered by our department, please see below our comments on:

1. Inclusion of ceftolozane/tazobactam (C/T) on the World Health Organization (WHO) Model List of Essential Medicines (EML) and the Model List of Essential Medicines for Children (EMLc)

General comments:

C/T is a novel β-lactam/β-lactamase inhibitor combination that was approved by the US Food and Drugs Administration (FDA) in 2019, for the treatment of hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP), caused by susceptible pathogens in patients 18 years and older. The FDA initially approved C/T in 2014 to treat complicated intra-abdominal infections (cIAIs) and for complicated urinary tract infections (cUTI), caused by susceptible organisms, in adults (18 and older). C/T was also approved by the European Medicines Agency (EMA) for treatment of: cIAIs; acute pyelonephritis; cUTIs; HAP, and VAP, in adults (18 and older).

Specific comments:

- In vitro studies suggest that C/T (ceftolozane) may have one of the best activities against Pseudomonas (e.g., The CANWARD study)[i].
- C/T demonstrated concentrations for both of its components exceeding the target concentrations for 100% of the dosing interval for both *Enterobacterales* and *P. aeruginosa*, in the lungs epithelial lining fluid of persons with pneumonia. Therefore, some national and regional guidelines (e.g., IDSA and ESCMID guidelines) recommend C/T beyond its approved indications, for the treatment of *P. aeruginosa* and MDR-P aeruginosa in the most recent based on currently limited but encouraging data [ii].
- Access: the applicant stated that C/T is registered in 79 countries globally, including 25 LMICs, with several additional on-patent filing pending including in 6 LMICs. The applicant also stated their intention to implement an access pricing framework for C/T.

In our view, the above supports the inclusion of ceftolozane + tazobactam (EML and EMLc), for the indications outlined above and in the application. Should the EML/EMLc committee agree with our recommendation, and in line with the WHO AWaRE classification of antibiotics, we recommend the classification of C/T in the Reserve Group of antibiotics that should only be used for treatment of confirmed or suspected infections due to multidrug-resistant organisms. We also stress that the use of C/T must be always informed by evidence-based guidance and strong stewardship activities. Access and affordability of the medicines including IMR must be considered, particularly for patients in LMICs.

2. Re: the inclusion of imipenem/cilastatin/relebactam on the World Health Organization (WHO) Model List of Essential Medicines (EML)

General comments:

IMR was approved by the US FDA, and (EMA) for the treatment of infections caused by susceptible Gram-negative bacteria in adult patients who have limited or no alternative treatment options, including the

treatment of cIAI, HAP, VAP, bacteremia, and cUTI including pyelonephritis, in adults (18 and older). Some national and regional guidelines recommend IMR as preferred treatment for the treatment of infections caused by some MDR Gram-negative bacteria in adult patients who have limited, or no alternative treatment options (based on limited data).

Specific comments:

- IMR meets the WHO innovation criterion of a novel chemical structure. Particularly, relebactam is a novel, non-beta-lactam bicyclic diazabicyclooctane β-lactamase inhibitor, which is combined with imipenem/cilastatin, for broader coverage. This means that the combination has the same activity as imipenem plus additional activity against many classes A and C β-lactamases including KCPs.[iii]
- IMR does not improve the activity of the carbapenem component (imipenem) against *Acinetobacter baumannii*, and it does not have activity against Class B carbapenemases.[iv]
- Access: the applicant stated that IMR is registered in 28 countries globally. The applicant also stated their intention to implement an access pricing framework for C/T.

In our view, the above supports the inclusion of IMR into the WHO EML, for the indications outlined above and in the application. Should the EML committee agree with this recommendation, and in line with the WHO AWaRE classification of antibiotics, we recommend the classification of IMR in the Reserve Group of antibiotics that should only be used for treatment of confirmed or suspected infections due to multidrug-resistant organisms. We stress that the use of IMR must be always informed by evidence-based guidance and strong stewardship activities. Access and affordability of the medicines including IMR must be considered, particularly for patients in LMICs.

3. Re: the inclusion of tedizolid phosphate on the World Health Organization (WHO) Model List of Essential Medicines (EML)

General comments:

Tedizolid was approved by the US Food and Drugs Administration (FDA) and by the by the European Medicines Agency (EMA), for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible Gram-positive organisms, in in adults and adolescents 12 years of age and older.

Specific comments:

- *Staphylococcus aureus* infections (including MRSA) is one of the most important causes of HAIs and AMR worldwide.
- Tedizolid is a novel oxazolidinone; once-daily does covers most Gram-positive organisms including VRE and MRSA. Result from an RCT showed that tedizolid was able to yield similar outcome for treatment of ABSSSI, over a shorter period of time (6-days) compared to linezolid (10-day regimen).
- In vitro studies reported activity against MRSA, including strains resistant to linezolid, or with reduced susceptibility to vancomycin. However, Tedizolid use should be avoided in invasive *S. aureus* infections (e.g., bacteremia, endocarditis) due to lack of clinical data.
- Tedizolids has low potential for clinically significant drug-drug interactions, with IV and oral formulations. It can be administered without the need for adjustment or monitoring in patients with renal impairment, hepatic impairment, obese patients, and elderly patients. This increases its utility especially in resource limited settings.
- Access: the applicant stated that tedizolid is currently registered in 43 countries globally. The applicant also stated their intention to implement an access pricing framework for tedizolid.

In our view, the above supports the inclusion of tedizolid into the WHO EML, for the indications outlined above and in the application. Tedizolid provides an option to addressing the unmet need for an anti-MRSA agent that can address infections due to vancomycin- intermediately susceptible and linezolid-resistant strains. Should the EML committee agree with this recommendation, and in line with the WHO AWaRE classification of antibiotics, we recommend classifying tedizolid in the "Reserve" group of antibiotics that should only be used for treatment of confirmed or suspected infections due to multidrug-resistant organisms. We stress that the use of tedizolid must be always informed by evidence-based guidance and strong stewardship activities. Access and affordability of the medicines including IMR must be considered, particularly for patients in LMICs.

4. **Re: The inclusion of amoxicillin/clavulanic acid 7:1 ratio dispersible tablet formulation on the World Health Organization (WHO) Model List of Essential Medicines for children (EMLc)**

General comments:

Amoxicillin trihydrate + Potassium Clavulanate 200 mg + 28.5 mg (7:1), pediatric quick tab is being as a therapeutic alternative to Amoxicillin + clavulanic acid 4:1 Powder for oral suspension, for the same indications. As described in the application, the benefits of the proposed formulation (dispersible tablet) compared to the currently included powder for oral suspension formulation include the stability of the dispersible tablet compared to the oral suspension across climate conditions; the practicality and feasibility for implementation of the dispersible tablet compared to the oral suspension that requires relatively more resources for its reconstitution; the dosing flexibility (the dispersible tablet can be dosed twice or thrice daily, depending on the severity of the infection and the causative pathogen) while existing oral preparations in the EMLc are in the 4:1 ratio, which requires 8 hourly dosing; and the lower frequency of adverse events.

In our view, the above supports the inclusion of the optimized formulation of amoxicillin/clavulanate (7:1 ratio dispersible tablet) to the EMLc, as a therapeutic alternative (to the 4:1 powder for oral suspension) for the same previously proposed indications, as outlined in the application. Access and affordability of the medicines including IMR must be considered, particularly for patients in LMICs.

5. **The inclusion of flomoxef sodium on the World Health Organization (WHO) Model List of Essential Medicines (EML) and the Model List of Essential Medicines for Children (EMLc)**

General comments:

- Flomoxef sodium (flomoxef) is being proposed for inclusion in the WHO EML for "empiric treatment of community-acquired mild/moderate intra-abdominal infections (IAI) (e.g., appendicitis, cholecystitis, diverticulitis) and mild/moderate upper urinary tract infections (UTI) (e.g., pyelonephritis), in adults and children at high risk of infection caused by ESBL-PE".
- Flomoxef is an old parenteral oxacephem antibiotic of the oxacephems subclass of second-generation cephalosporins, approved in Japan, China, Taiwan, and South Korea since 1988 for use in adults and children for treatment of susceptible Gram-positive and Gram-negative infections.
- Recent in vitro data presented suggest that flomoxef is active against some ESBLs and some narrow spectrum β-lactamases. Based largely on in vitro data, flomoxef is being proposed as "carbapenem-sparing option for the treatment/management of resistant bacterial infections caused by ESBL-PE infections, including empiric treatment of community acquired infections".

- As acknowledged by the applicant, the quality of evidence presented is not consistently rigorous mainly since most of the clinical trials were done between 1988-2000, and the current evidence does not support flomoxef use as monotherapy in situations with high burden infections and more data is needed for these indications particularly with optimized regimens.

Specific comments:

- Two recent in vitro studies conducted by GARDP reported a strong in vitro activity of flomoxef against clinical isolates of ESBL-PE from different regions, which might support the consideration of the antibiotic as a potential carbapenem-sparing treatment for infections due to ESBL-PE. However, more in vivo surveillance data from the clinical setting are not available. Further, as most of the major RCTs were conducted before 2000, the targeted systematic reviews reported in the application did not reported activity against ESBL-PE infections from these studies.
- The application report that the studies reviewed "*show that the appropriateness of flomoxef as single treatment option for bacteremia seems to depend on the MIC and the severity of disease".* As noted previously, currently there is no minimum MIC breakpoint available for flomoxef, and therefore, latamoxef/moxalactam MIC breakpoint (available from CLSI) is used instead. The applicant points out that the "*overall assessment currently supports the exclusion of flomoxef use as monotherapy for empiric treatment of high-burden infections that can lead to sepsis but does not rule out a possible use in combination or use as monotherapy at higher doses in the future. Further studies are needed to support these indications".*
- Post marketing data in the application indicate that, while the overall cure rate in mild and moderate infections was good, "*flomoxef monotherapy showed lower efficacy with increasing severity, for almost all indications including the indication of bloodstream/systemic infections suggesting that this agent on its own may not be ideal in cases with severe and high burden infections*".
- The inclusion of Flomoxef in evidence-based government guidelines, as well as guidelines endorsed by the community of practice in countries with robust healthcare systems like Japan, south Korea and Taiwan is encouraging. The data used to inform these guidelines are likely local and more relevant to the context/patient populations in these countries. We encourage the EML committee to consider and review the evidence used to inform such guidelines, including its adequacy and applicability to other regions/contexts.
- Flomoxef is administered parenterally as an injection or IVI (no oral formulation). It administered on a mg/kg basis; each daily dose must be infused over at least 30 min for up to 4 doses a day. This has the advantage that age-appropriate formulations are not needed. However, the administration of the medicine requires access to a healthcare facility with expertise for making the diagnosis, accurate dosing, and optimization of antibiotic therapy, including in children and neonates; capacity for reconstitution, administration, and storage of antibiotic suspension formulations, including frequent IV infusions; and capacity for infection prevention and control. These requirements might not be available, affordable and/or accessible to many patients in resources-limited settings. It is important to note that this is not unique to flomoxef and that other medicines in the EML have similar barriers.
- Pricing, cost-effectiveness and access (market availability): While we appreciate considerations of affordability and access in the application, no comparative pricing analyses was presented for LMICs. Estimates from Spain were used as proxy for LMICs, but the application acknowledges that *prices are likely expected to be higher in most LMICs*. Further, with marketing, manufacturing, and production

based exclusively Asia (4 countries), expansion of access globally, and ensuring affordable and sustainable access especially in LMICs, is not clear.

We acknowledge that flomoxef sodium could have an added role in the treatment of the indications outlined globally. We also note that this product could potentially be a viable carbapenem-sparing option for the treatment/management of resistant bacterial infections caused by ESBL-PE infections, especially in settings where the prevalence of ESBL-PE is high. However, more in vivo data are needed to support its inclusion into the 2023 EML/EMLc. Additionally, we would like to note that this drug may be of interest for the management of neonatal sepsis. However, a determination in this regard is likely premature currently. Flomoxef sodium could be considered for inclusion in future EML/EMLc once more data become available including from the ongoing GARDP neonatal sepsis trials.

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[i] Walkty A, Karlowsky JA, Adam H, Baxter M, Lagacé-Wiens P, Hoban DJ, Zhanel GG. In vitro activity of ceftolozane-tazobactam against Pseudomonas aeruginosa isolates obtained from patients in Canadian hospitals in the CANWARD study, 2007 to 2012. Antimicrob Agents Chemother. 2013 Nov;57(11):5707-9. doi: 10.1128/AAC.01404-13. Epub 2013 Aug 12. PMID: 23939895; PMCID: PMC3811242.

[ii] Zhanel GG, Chung P, Adam H, Zelenitsky S, Denisuik A, Schweizer F, Lagacé-Wiens PR, Rubinstein E, Gin AS, Walkty A, Hoban DJ, Lynch JP 3rd, Karlowsky JA. Ceftolozane/tazobactam: a novel cephalosporin/β-lactamase inhibitor combination with activity against multidrug-resistant gram-negative bacilli. Drugs. 2014 Jan;74(1):31-51. doi: 10.1007/s40265-013-0168-2. PMID: 24352909.

[iii] Haidar G, Clancy CJ, Chen L, Samanta P, Shields RK, Kreiswirth BN, Nguyen MH. Identifying Spectra of Activity and Therapeutic Niches for Ceftazidime-Avibactam and Imipenem-Relebactam against Carbapenem-Resistant Enterobacteriaceae. Antimicrob Agents Chemother. 2017 Aug 24;61(9):e00642-17. doi: 10.1128/AAC.00642-17. PMID: 28630202; PMCID: PMC5571343.

[iv] Lapuebla A, Abdallah M, Olafisoye O, Cortes C, Urban C, Landman D, Quale J. Activity of Imipenem with Relebactam against Gram-Negative Pathogens from New York City. Antimicrob Agents Chemother. 2015 Aug;59(8):5029-31. doi: 10.1128/AAC.00830-15. Epub 2015 May 26. PMID: 26014931; PMCID: PMC4505292.