Eravacycline

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.3. Reserve group antibiotics

ATC codes: J01AA13

Indication	Other carbapenem resistant Enterobacterales ICD11 code: MG50.C0
INN	Eravacycline
Medicine type	Chemical agent
Antibiotic groups	R RESERVE
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 50 mg lyophilized powder for injection
EML status history	Application rejected in 2019 (TRS 1021)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Read more about patents.
Wikipedia	Eravacycline
DrugBank	Eravacycline

Expert Committee recommendation

The Expert Committee did not recommend the addition of eravacycline to the EML. The Committee considered that although eravacycline demonstrates activity against some strains of carbapenemase-producing Enterobacteriaceae, there are some concerns with regard to efficacy, as eravacycline failed to demonstrate non-inferiority compared to levofloxacin in one RCT for cUTI. In addition, the Committee considered that there could be safety concerns, with no long-term safety data currently available. The Committee noted pharmacological similarities between eravacycline and tigecycline, and the reported increased mortality associated with tigecycline in some meta-analyses. The Expert Committee agreed with the EML Antibiotic Working Group's recommendation that eravacycline be classified in the AWaRe Reserve group.

Background

The application requested the inclusion of eravacycline on the complementary list of the EML as a last-resort treatment option for infections due to multidrugresistant organisms (MRDOs). Eravacycline had not previously been considered for inclusion on the EML. Eravacycline is a fully synthetic tetracycline antibiotic that has a spectrum of activity similar to tigecycline and maintains its activity in the presence of two common resistance mechanisms: ribosomal protection and active drug efflux. It retains activity against most ESBL producing Enterobacteriaceae and some strains of carbapenem-resistant Enterobacteriaceae and Acinetobacter baumannii but has limited activity against Pseudomonas aeruginosa (1–4).

Public health relevance

Antibiotic-resistant bacteria are a significant threat to public health, both in HICs as well as LMICs (5–7). A recent study estimated that infections with antibioticresistant bacteria were responsible for approximately 33 000 attributable deaths in Europe in 2015 (5). Fewer data are available for LMICs, but a retrospective study in ten hospitals in India found that resistant pathogens were associated with two to three times higher mortality than infections with susceptible strains after adjusting for several confounders (6). Over the past decade there has been increasing spread of multidrugresistant Gram-negative pathogens such as carbapenemase producing Enterobacteriaceae (8). The Global Antimicrobial Resistance Surveillance System (GLASS) report published in 2018 found high levels of carbapenem resistance in Enterobacteriaceae and non-fermenters in many of the LMICs providing data for the report (6). The 2015 WHO Global action plan on antimicrobial resistance calls for the development of new antimicrobial medicines (7). To provide a framework for this endeavour, in 2017 WHO published a priority list of antibiotic-resistant bacteria (9). “Priority 1: critical” category includes four types of pathogens, all of which are Gram-negative: carbapenem resistant Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacteriaceae; and third-generation cephalosporin-resistant Enterobacteriaceae (10).

Benefits

Eravacycline achieved the predefined criteria for non-inferiority compared with ertapenem in one trial and meropenem in another trial in the treatment of cIAI in hospitalized adults (11, 12). A further trial has been conducted in adult patients with cUTI using levofloxacin as comparator, but the results have so far only been published on cinicaltrials.gov (NCT01978938) and eravacycline “did not achieve its primary endpoint of statistical non-inferiority compared to levofloxacin” (13). Like for other tetracyclines, eravacycline use is not recommended in children younger than 8 years and pregnant or breastfeeding women due to the risk of tooth discoloration and enamel hypoplasia. A Phase I multicentre study to assess the pharmacokinetics and safety of intravenous (IV) eravacycline in children aged 8 to 18 years is currently recruiting patients (ClinicalTrials.gov Identifier: NCT03696550).

Harms

In the trials comparing eravacycline to a carbapenem (ertapenem and meropenem respectively) more treatment-emergent AEs were observed in the eravacycline treatment groups (11, 12). The difference was mostly attributable to nausea and phlebitis.

Cost / cost effectiveness

United States: wholesale acquisition cost of US$ 175 per day of treatment (14). No cost-effectiveness data are available.

WHO guidelines

There are no available WHO guidelines for the treatment of infections due to MDROs.

Availability

Eravacycline has been approved in the United States and the European Union for the treatment of cIAI in adults.

Other considerations

Safety concerns exist for tigecycline, a pharmacologically similar agent with a similar spectrum of activity to eravacycline, with an increased risk of mortality compared with other antimicrobials being reported (15–17). The FDA issued a boxed warning about this risk in 2013 (18). In a separate recommendation made during the meeting, the Expert Committee recommended the removal of tigecycline from the EML and EMLc.

1. Livermore DM, Mushtaq S, Warner M, Woodford N. In Vitro Activity of Eravacycline against Carbapenem-Resistant Enterobacteriaceae and Acinetobacter baumannii. Antimicrob Agents Chemother. 2016;60(6):3840–4.
2. Seifert H, Stefanik D, Sutcliffe JA, Higgins PG. In-vitro activity of the novel fluorocycline eravacycline against carbapenem non-susceptible Acinetobacter baumannii. Int J Antimicrob Agents. 2018;51(1):62–4.
3. Zhanel GG, Baxter MR, Adam HJ, Sutcliffe J, Karlowsky JA. In vitro activity of eravacycline against 2213 Gram-negative and 2424 Gram-positive bacterial pathogens isolated in Canadian hospital laboratories: CANWARD surveillance study 2014-2015. Diagn Microbiol Infect Dis. 2018;91(1):55–62.
4. Zhanel GG, Cheung D, Adam H, Zelenitsky S, Golden A, Schweizer F, et al. Review of Eravacycline, a Novel Fluorocycline Antibacterial Agent. Drugs. 2016;76(5):567–88.
5. Cassini A, Hogberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019; 19(1):56–66.
6. Gandra S, Tseng KK, Arora A, Bhowmik B, Robinson ML, Panigrahi B, et al. The mortality burden of multidrug-resistant pathogens in India: a retrospective observational study. Clin Infect Dis. 2019; 69(4): 563–570.
7. Global action plan on antimicrobial resistance. Geneva: World Health Organization; 2015. Available from: https://apps.who.int/iris/handle/10665/311820, accessed 30 October 2019.
8. van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence. 2017;8(4):460–9.
9. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017. Available from: https://apps.who.int/iris/handle/10665/311820, accessed 30 October 2019.
10. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318–27.
11. Solomkin J, Evans D, Slepavicius A, Lee P, Marsh A, Tsai L, et al. Assessing the Efficacy and Safety of Eravacycline vs Ertapenem in Complicated Intra-abdominal Infections in the Investigating GramNegative Infections Treated With Eravacycline (IGNITE 1) Trial: A Randomized Clinical Trial. JAMA Surg. 2017;152(3):224–32.
12. Solomkin JS, Gardovskis J, Lawrence K, Montravers P, Sway A, Evans D, et al. IGNITE4: Results of a Phase 3, Randomized, Multicenter, Prospective Trial of Eravacycline vs. Meropenem in the Treatment of Complicated Intra-Abdominal Infections. Clin Infect Dis. 2019;69(6):921–929.
13. Tetraphase Pharmaceuticals Inc. (2015). Tetraphase announces top-line results from IGNITE2 phase 3 clinical trial of eravacycline in cUTI [website]. (https://ir.tphase.com/news-releases/news-release-details/tetraphase-announces-top-line-results-ignite2-phase-3-clinical, accessed 20 March 2019).
14. Tetraphase Pharmaceuticals Inc. (2018). Tetraphase Pharmaceuticals announces commercial launch of Xerava in the United States [website]. (https://ir.tphase.com/news-releases/newsrelease-details/tetraphase-pharmaceuticals-announces-commercial-launch-xeravatm, accessed 20 March 2019).
15. McGovern PC, Wible M, El-Tahtawy A, Biswas P, Meyer RD. All-cause mortality imbalance in the tigecycline phase 3 and 4 clinical trials. Int J Antimicrob Agents. 2013;41(5):463–7.
16. Shen F, Han Q, Xie D, Fang M, Zeng H, Deng Y. Efficacy and safety of tigecycline for the treatment of severe infectious diseases: an updated meta-analysis of RCTs. Int J Infect Dis. 2015;39:25–33.
17. Prasad P, Sun J, Danner RL, Natanson C. Excess deaths associated with tigecycline after approval based on noninferiority trials. Clin Infect Dis. 2012;54(12):1699–709.
18. US Food and Drug Administration (2013). FDA Drug Safety Communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecyclne) and approves new Boxed Warning [website]. (https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safetycommunication-fda-warns-increased-risk-death-iv-antibacterial-tygacil-tigecycline, accessed 20 March 2019).

