NICE National Institute for Health and Care Excellence

Antimicrobial prescribing: eravacycline for complicated intra-abdominal infections in adults

Evidence review

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This evidence review sets out the best available evidence on eravacycline for treating complicated intra-abdominal infections. It should be read in conjunction with the evidence summary, which gives the likely place in therapy and factors for decision making.

Disclaimer

The content of this evidence review was up to date in March 2022. See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

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Contents

Background

Intra-abdominal infections include a wide spectrum of conditions, from uncomplicated appendicitis to faecal peritonitis. In complicated intra-abdominal infections, the infection progresses from a single organ and affects the peritoneum, causing intra-abdominal abscesses or diffuse peritonitis. Peritoneal contamination may result from surgery-associated infection, trauma or spontaneous perforation (for example, appendicitis, perforated ulcer or diverticulitis).

Complicated intra-abdominal infections represent the second most common cause of morbidity and mortality after pneumonia in the intensive care unit (ICU), and remain responsible for 20% of the severe sepsis cases in the ICU. Among patients who develop persistent or recurrent hospital-acquired complicated intra-abdominal infections following apparently successful surgical source control, mortality may exceed 50%.(European Medicines Agency [EMA] European public assessment report)

Effective management of complicated intra-abdominal infection requires early diagnosis, appropriate surgical intervention and empiric, broad-spectrum, antimicrobial treatment.

The pathogens most frequently seen in complicated intra-abdominal infections are the Gram-negative bacteria *Escherichia coli*, other common *Enterobacteriaceae*, *Pseudomonas aeruginosa and Bacteroides fragilis*. Second or third generation cephalosporins in combination with metronidazole; beta-lactam antibiotics (such as penicillins) in combination with beta-lactamase inhibitors; and carbapenems are commonly used for treating complicated intra-abdominal infections. However, increasing resistance to commonly prescribed antimicrobial agents is a recognised serious global problem (European Medicines Agency [EMA] European public assessment report). The English surveillance programme for antimicrobial utilisation and resistance report (2020 to 2021) states that *Escherichia coli* was the most common cause of bloodstream infection in 2016 to 2020. There was an incidence of 73 per 100,000 population in 2016, increasing to around 78 per 100,000 in 2019, and declining to 66.9 per 100,000 in 2020. This decrease is thought to be due to pandemic-associated reduction in person-to-person contact although the underlying

causes are likely to be complex and multifactorial. The report does not include data specifically for complicated intra-abdominal infections.

NICE has not published any guidance on complicated intra-abdominal infections, although there are recommendations on antibiotics for acute diverticulitis in the NICE guideline on diverticular disease.

Information can also be found in guidelines by the Surgical Infection Society and the Infectious Diseases Society of America and the World Society of Emergency Surgery. These recommend empirical antibiotic treatment with single or combination antimicrobial regimens depending on the severity of infection, the pathogens presumed to be involved (taking into account whether the infection is community- or healthcare-associated) and local antibiotic resistance patterns. The guidelines state that bacteriological cultures often have little impact on the course of treatment and are not necessary for all patients. However, results of microbiological analysis of intra-abdominal samples can be used to customise antibiotic treatment and ensure adequate antimicrobial activity in high-risk patients who may have resistant pathogens, and in people in whom the causative pathogens and related resistance patterns are not predictable.

This evidence summary outlines the best available evidence for eravacycline, a new antimicrobial that is licensed for treating complicated intra-abdominal infections in adults.

Product overview

Mode of action

Eravacycline (Xerava) is a tetracycline and works by binding and blocking part of the cell machinery in bacterial cells that is involved in making proteins. This leads to death of the bacteria causing the infection (EMA European public assessment report).

Regulatory status

Eravacycline (Xerava, PAION Deutschland GmbH) has a marketing authorisation for treating complicated intra-abdominal infections in adults, which was granted in the UK in January 2021 (summary of product characteristics [SPC]).

Dosing information

Eravacycline is available as a vial containing 100 mg powder for concentrate for solution for infusion.

The recommended dose regimen is 1 mg/kg administered over 1 hour, every 12 hours for 4 to 14 days (SPC).

Antimicrobial resistance

Resistance to eravacycline has been observed in Enterococcus harbouring mutations in the rpsJ gene. There is no target-based cross-resistance between eravacycline and other classes of antibiotics such as quinolones, penicillins, cephalosporins and carbapenems. Other bacterial resistance mechanisms that could potentially affect eravacycline are associated with upregulated, non-specific intrinsic multidrug-resistant efflux (SPC).

Objective

This evidence summary aims to review the best available evidence on the effectiveness and safety of eravacycline for treating complicated intra-abdominal infections in adults.

Review questions

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review questions for this evidence review are:

1. What is the effectiveness of eravacycline for the treatment of complicated intra-abdominal infections in adults?

2. What is the safety of eravacycline for the treatment of complicated intra-abdominal infections in adults?

Summary of included studies

A literature search for eravacycline for the treatment of complicated intra-abdominal infections identified 116 references (see appendix E for full details). These references were screened using their titles and abstracts, and 18 full text references were obtained and assessed for relevance.

Two studies are included in this evidence summary. A summary of the included studies is shown in appendix B. Quality assessment of the included studies is in appendix C.

The 2 studies (Solomkin et al. 2017 and Solomkin et al. 2019) are phase 3 double-blinded, placebo-controlled randomised controlled trials (RCTs). Solomkin et al. (2017; n=541) compared intravenous eravacycline with intravenous ertapenem.

Solomkin et al. (2019) (n=500) compared intravenous eravacycline with intravenous meropenem. The participants in both studies were aged 18 years or older and were hospitalised for complicated intra-abdominal infections.

16 studies were excluded. Details of these excluded studies are in appendix F.

Effectiveness and safety

Full details of the results are in appendix D.

Review question 1: What is the effectiveness of eravacycline for the treatment of complicated intra-abdominal infections in adults?

Clinical response at test of cure

In both studies assessment of this outcome was categorised as clinical cure, clinical failure or indeterminate/missing. In the modified intention to treat (MITT) population (adults who received at least 1 dose of intervention or comparator), intravenous eravacycline was non-inferior to intravenous ertapenem (Solomkin et al. 2017) and meropenem (Solomkin et al. 2019) for the outcome of clinical cure, assessed 25 to

31 calendar days after the first dose of the study drug was administered. In Solomkin et al. (2017), if the lower limit of the 95% CI for the difference in clinical cure rates were greater than −10%, non-inferiority was achieved. For Solomkin et al. (2019), a non-inferiority margin of 12.5% was agreed, which represents the standard margin for the European Medicines Agency.

In Solomkin et al. (2017) in the MITT population, 235/270 (87.0%) participants in the eravacycline group had response of clinical cure compared with 238/268 (88.8%) in the ertapenem group (difference 1.8%, 95% CI −7.4% to 3.8%).

In Solomkin et al. (2019) in the MITT population, 231/250 (92.4%) participants in the eravacycline group had response of clinical cure compared with 228/249 (91.6%) in the meropenem group (difference +0.8%, 95% CI −4.1% to 5.8%).

Similar results were found for clinical cure in the micro-ITT (microbiological intent-to-treat) population for both studies.

Clinical response by baseline pathogen

In Solomkin et al. (2017) and in Solomkin et al. (2019), the percentage of clinical cure was similar between treatment groups for most pathogens.

Review question 2: What is the safety of eravacycline for the treatment of complicated intra-abdominal infections in adults?

Adverse events were seen in 113/270 (41.9%) of participants given eravacycline and 75/268 (28.0%) of participants given ertapenem (Solomkin et al. 2017). Serious adverse events occurred in 13/270 (4.9%) of participants in the eravacycline group and 13/268 (4.8%) in the ertapenem group.

In Solomkin et al. (2019) adverse events were seen in 93/250 (37.2%) of participants given eravacycline and 77/249 (30.9%) of participants given meropenem.

The summary of product characteristics (SPC) for eravacycline lists the following common adverse reactions (seen in between 1 in 10 and 1 in 100 people): thrombophlebitis, phlebitis, nausea, vomiting and infusion site reactions. See the

SPC for eravacycline for full details on adverse events, contraindications, warnings and precautions for use.

Limitations of the evidence

Both studies (Solomkin et al. 2017 and Solomkin et al. 2019) were well conducted placebo controlled, double-blind, multicentre randomised controlled trials which were assessed as having low risk of bias. Both studies compared eravacycline with carbapenems which are currently used in practice to treat complicated intra-abdominal infections.

Both intention-to-treat and per-protocol analyses were undertaken, and their results were consistent, as required to demonstrate non-inferiority (see European Medicines Agency guidance on points to consider on switching between superiority and non-inferiority). In the paper by Solomkin et al. (2017), the stated primary objective was to demonstrate non-inferiority of eravacycline compared with ertapenem for clinical cure rates at the test-of-cure visit in the MITT. However, to meet the requirements of the European Medicines Agency, the primary analysis considered the clinically evaluable population. In the Solomkin et al. (2019) paper, which compared eravacycline with meropenem, the primary objective, as agreed by the United States Food and Drug Administration (FDA), was clinical cure at the test-of-cure visit in the micro-ITT population. Clinical cure in the clinically evaluable population, which was the European Medicines Agency-required outcome, was the secondary outcome. Again, the results were consistent across both populations.

As eravacycline had demonstrated non-inferiority at a 10% non-inferiority margin in the Solomkin et al. (2017) study, a non-inferiority margin of 12.5% was used in Solomkin et al. (2019) as agreed by the FDA. This is the standard margin for the European Medicines Agency.

The studies have various limitations that should be taken into account when considering their application to practice. Most of participants were white (over 95% in both studies), and about 70% were aged 65 or younger in both studies. Solomkin et al. (2017) reported an APACHE II (a mortality prediction tool) mean score of 6.7 and Solomkin et al. (2019) reported a mean score of 6.6 suggesting a low risk of

mortality. Therefore, the results may not be generalisable to older adults who are at a higher risk of dying, with higher APACHE II scores.

Both studies met the pre-specified upper limit of patients randomised with complicated appendicitis. This was set at 50% in Solomkin et al. (2019) and 30% in the Solomkin et al. (2017) study. However, the 50% limit set by Solomkin et al. (2019) was not in line with the practice advised by the Committee for Medicinal Products for Human Use, which states that the percentage of patients with complicated appendicitis should be limited to 30%. It is not known if this would have had an impact on the results. Eravacycline has not been studied in children and is only indicated for use in adults.

Person-centred factors

Eravacycline is given as an intravenous infusion only, over approximately 1 hour. The recommended dose is 1 mg/kg eravacycline every 12 hours for 4 to 14 days. In practice, it is highly likely to be prescribed and administered in a hospital setting.

Specialists who commentated on this evidence review highlighted that in practice eravacycline is likely to be prescribed for people who are allergic to penicillin or when standard intravenous antibiotics are not suitable or have been ineffective.

Eravacycline has a marketing authorisation for treating adults only and there is no requirement to adjust the dose for age, weight, or mild to moderate renal function.

Resource implications

The cost of eravacycline 100 mg powder for concentrate for solution for infusion is £105 for 1 vial (see MIMS, May 2022). The cost of a treatment course based on an average weight of 75 kg and assuming part vials are not stored or shared is £840 to £2,940 for 4 to 14 days, respectively.

In comparison, the cost of ertapenem 1g powder for solution for infusion in March 2022 was £31.65 for 1 vial (see the Drug Tariff). The cost of a treatment course for 4 to 14 days is £127 to £443.

The cost of meropenem 1g powder for solution for injection in March 2022 was £20.38 for 1 vial (see the Drug Tariff). The cost of a treatment course for 4 to 14 days is £245 to £856.

This cost is for the medicine only and does not include any associated costs related to antibiotic administration in hospital.

References

Solomkin J, Gardovskis J, Lawrence K et al. (2019) IGNITE4: Results of a phase 3, randomized, multicenter, prospective trial of eravacycline vs meropenem in the treatment of complicated intraabdominal infections. Clinical infectious diseases 69(6): 921-929

Solomkin J, Evans D, Slepavicius A et al. (2017) Assessing the efficacy and safety of eravacycline vs ertapenem in complicated intra-abdominal infections in the Investigating Gram-Negative Infections Treated With Eravacycline (IGNITE 1) trial: a randomized clinical trial. JAMA surgery 152(3): 224-232

Development of the evidence review

Process

The evidence summaries: process guide sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

Expert advisers

Details of expert advisers and any declarations of interest

Name, job title and organisation	Declaration of interest
David Humes Consultant Colorectal Surgeon, Nottingham University Hospitals NHS Trust and Clinical Associate Professor in GI Surgery, University of Nottingham	No relevant interests declared
Natasha Ratnaraja Consultant Microbiologist, University Hospitals Coventry and Warwickshire NHS Trust	Microbiologist for BMI Meriden healthcare providing clinical advice (Financial interest October 2018 – ongoing)

Name, job title and organisation	Declaration of interest
	Council member British Infection Association (Non-financial interest September 2016 – ongoing) Reviewer for NICE (Non-financial interest October 2019 – ongoing) Deputy Chair Medical Microbiology & Virology SAC, RCPath (non-financial interest, April 2021-Ongoing) Member of RCPath COVID Action Group (non-financial interest November 2020-Ongoing) BIA representative on SMI bacteriology working group (non-financial interest June 2021-Ongoing) Affiliate member of ID CRG (non-financial interest January 2021 – Ongoing)
Colin Brown Deputy Director (Interim), Healthcare-associated Infections and Antimicrobial Resistance, National Infection Service, UK Health Security Agency	Microbiologist to a private charitable hospital with onsite hospice (financial interest -January 2020-Ongoing) Ad hoc one-off market research advisory, no long-term engagements or direct communication with pharmaceutical companies (though some relate to antibiotics) (financial interest -2012-ongoing) Occasional contact with companies promoting novel antimicrobial therapies through role with AMRHAI (antimicrobial resistance and healthcare associated infections) as the national reference laboratory for investigating AMR in healthcare-associated bacteria. (non-financial interest April 2019-ongoing) Gilead Sciences reimbursed Public Health England for the time given in delivering an educational update on C. auris at a fungal conference they organised. (non-financial interest – Sep 2017 – Oct 2018) Part of an ad-hoc and unofficial group of interested experts met in London to review available data and identify monkeypox-related research gaps, convened by Bavarian Nordic, manufacturer of a vaccine registered as Jynneos for smallpox and monkeypox indications in the USA (Imvanex for smallpox only in Europe and Imvamune for smallpox only in Canada). (non-financial interest June 2019 – June 2019) Attend Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI) and the Antimicrobial Programme Board on behalf of Public Health England (non-financial interest-April 2019 – ongoing)
Alicia Demirjian	UK Paediatric Antimicrobial Stewardship network: lead (Non-financial interest, 2019-ongoing)

Name, job title and organisation	Declaration of interest
Consultant epidemiologist, UK Health Security Agency; Consultant in paediatric infectious diseases, Evelina London Children's Hospital	Employee of the UK Health Security Agency and National Health Service (Non-financial interest 2016 -ongoing)

Terms used in this evidence review

Clinical cure

Complete resolution or significant improvement of signs or symptoms of the index infection such that no additional antibacterial therapy, surgical, or radiological intervention (for example, ultrasound-guided drainage) is required.

APACHE II

Acute Physiology and Chronic Health Evaluation; This is a scoring system (scale of 0 to 71) that uses a point score based upon initial values of 12 routine physiologic measurements, age, and previous health status to provide a general measure of severity of disease. Lower scores are better (Knaus et al. 1985).

Appendices

Appendix A: PICO table

PICO table

Criteria	Details
P – Population and indication	Adults aged 18 years and over who have cIAI.
I – Intervention	Eravacycline (Xerava) 1 mg/kg every 12 hours. Administered as intravenous infusions over approximately 60 minutes every 12 hours. The recommended duration of treatment for cIAI is 4 to 14 days.
C – Comparator(s)	Any comparator
O – Outcomes	Clinical response Microbiological response Adverse events
Inclusion criteria	-
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, observational studies including case series If no higher-level quality evidence is found, observational studies including case series can be considered
Language	English
Patients	Human studies only
Age	Adults 18 years and over
Date limits	None
Exclusion criteria	-
Publication type	Pre-prints prior to peer review, letters, conference abstracts or studies that have not been published in full
Study design	Case reports

Abbreviations: cIAI, complicated intra-abdominal infection

Appendix B: Summary of included studies

Summary of included studies

Study	Number of participants	Population	Intervention	Comparison	Outcomes
Solomkin et al. (2017) RCT Multicentre	n=541	Adults 18 years or older with clinical evidence of cIAI needing urgent surgery or PCI within 48 hours of diagnosis	Intravenous infusion of eravacycline, 1 mg/kg every 12 hours (n=270)	Intravenous infusion of ertapenem, 1 g every 24 hours (n=271)	Primary outcome: Clinical response at the test-of-cure visit Key secondary outcomes: Microbiological response Adverse events
Solomkin et al. (2019) RCT Multicentre	n=500	Adults 18 years or older with clinical evidence of cIAI needing surgery or PCI	Intravenous infusion of eravacycline, 1 mg/kg every 12 hours (n=250)	Intravenous infusion of meropenem, 1 g every 8 hours (n=250)	Primary outcome: Clinical response at the test-of-cure visit Key secondary outcomes: Microbiological response Adverse events

Abbreviations: cIAI, complicated intra-abdominal infection; PCI, percutaneous intervention; RCT, randomised controlled trial

Appendix C: Quality assessment of included studies

Quality assessment of Solomkin et al. (2017)

Question	Solomkin et al. (2017)
Domain 1: Risk of bias arising from the randomisation process	-
1.1 Was the allocation sequence random?	Yes
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
Risk of bias judgement	Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	-
2.1. Were participants aware of their assigned intervention during the trial?	No
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	-
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	-
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	-
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	-
Risk of bias judgement	Low
Domain 3: Missing outcome data	-
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	No
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Yes
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	No
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	-
Risk of bias judgement	Low
Domain 4: Risk of bias in measurement of the outcome	-

Question	Solomkin et al. (2017)
4.1 Was the method of measuring the outcome inappropriate?	No
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably no
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	-
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	-
Risk of bias judgement	Low
Domain 5: Risk of bias in selection of the reported result	-
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis?	Probably yes
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Probably no
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	Probably no
Risk of bias judgement	Low
Overall risk of bias judgement	Low

Checklist used: Cochrane risk of bias 2 tool.

Abbreviations: Y, yes; PY, probably yes; PN, probably no; N, no; NI, no information.

Quality assessment of Solomkin et al. (2019)

Question	Solomkin et al. (2019)
Domain 1: Risk of bias arising from the randomisation process	-
1.1 Was the allocation sequence random?	Yes
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
Risk of bias judgement	Low

Question	Solomkin et al. (2019)
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	-
2.1. Were participants aware of their assigned intervention during the trial?	No
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	-
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	-
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	-
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	-
Risk of bias judgement	Low
Domain 3: Missing outcome data	-
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	No
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Yes
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	No
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	-
Risk of bias judgement	Low
Domain 4: Risk of bias in measurement of the outcome	-
4.1 Was the method of measuring the outcome inappropriate?	No
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably no
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	-
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	-
Risk of bias judgement	Low

Question	Solomkin et al. (2019)
Domain 5: Risk of bias in selection of the reported result	-
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis?	Probably yes
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Probably no
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	Probably no
Risk of bias judgement	Low
Overall risk of bias judgement	Low

Checklist used: Cochrane risk of bias 2 tool.

Abbreviations: Y, yes; PY, probably yes; PN, probably no; N, no; NI, no information.

Appendix D: Results tables

Results table for Solomkin et al. (2017)

Outcome	Intervention	Comparator	Analysis
Primary outcome	**n=270**	**n=268**	**-**
Clinical cure at the test-of-cure visit (MITT)	235 (87.0%)	238 (88.8%)	−1.80% (95% CI −7.4% to 3.8% [non-inferior])
Secondary outcomes	**n=220**	**n=226**	**-**
Clinical cure at the test-of-cure visit (micro-ITT)	191 (86.8%)	198 (87.6%)	−0.80% (95%CI −7.1% to 5.5% [non-inferior])
Subgroup analysis by baseline pathogen	-	-	-
Clinical cure at the test-of-cure visit – *Escherichia Coli*	109/127 (85.8%)	112/132 (84.8%)	No statistical analysis reported
Clinical cure at the test-of-cure visit – *Pseudomonas Aeruginosa*	15/18 (83.3%)	18/20 (90.0%)	No statistical analysis reported
Clinical cure at the test-of-cure visit – *Bacteroides Fragilis*	39/44 (88.6%)	38/42 (90.5%)	No statistical analysis reported
Safety outcomes	**n=270**	**n=268**	-
Any adverse event	113/270 (41.9%)	75/268 (28.0%)	No statistical analysis reported
Serious adverse events	13/270 (4.8%)	13/268 (4.9%)	No statistical analysis reported
Nausea	22/270 (8.1%)	2/268 (0.7%)	No statistical analysis reported
Phlebitis at infusion site	8/270 (3.0%)	1/268 (0.4%)	No statistical analysis reported

Abbreviations: CI, confidence interval; micro-ITT, microbiological intention to treat; MITT, modified intention to treat population

Clinical cure was defined as complete resolution or significant improvement of signs or symptoms of the index infection such that no additional antibacterial therapy, surgical, or radiological intervention was required. Clinical cure at the test-of-cure visit (25 to 31 days after first dose of the study drug) was assessed by noninferiority of eravacycline to ertapenem. It was assessed by using the lower limit of the 95% CI for between group differences being at least −10%.

Modified ITT analysis (MITT), includes only the people who have taken at least 1 dose of the study drug. Micro-ITT analysis includes people who had baseline bacterial pathogens against at least 1 of which the study drug had in vitro antibacterial activity.

Results table for Solomkin et al. (2019)

Outcome	Intervention	Comparator	Analysis
Primary outcome	**n=195**	**n=205**	**-**
Clinical cure at the test-of-cure visit (micro-ITT)	177 (90.8%)	187 (91.2%)	−0.5% (95%CI −6.3% to 5.3% [non-inferior])
Secondary outcomes	**n=250**	**n=249**	**-**
Clinical cure at the test-of-cure visit (MITT)	231 (92.4%)	228 (91.6%)	+0.8% (95%CI −4.1% to 5.8% [non-inferior])
Subgroup analysis by baseline pathogen	-	-	-
Clinical cure at the test-of-cure visit – *Escherichia Coli*	111/126 (88.1%)	125/134 (93.3%)	No statistical analysis reported
Clinical cure at the test-of-cure visit – *Pseudomonas Aeruginosa*	18/19 (94.7%)	18/20 (90.0%)	No statistical analysis reported
Clinical cure at the test-of-cure visit – *Bacteroides Fragilis*	33/40 (82.5%)	35/38 (92.1%)	No statistical analysis reported
Safety outcomes	**n=250**	**n=249**	-
Any adverse event	93/250 (37.2%)	77/249 (30.9%)	No statistical analysis reported
Nausea	12/250 (4.8%)	2/249 (0.8%)	No statistical analysis reported
Phlebitis at infusion site	8/250 (3.2%)	1/249 (0.4%)	No statistical analysis reported

Abbreviations: CI, confidence interval; micro-ITT, microbiological intention to treat; MITT, modified intention-to-treat population;

Clinical cure was defined as complete resolution or significant improvement of signs or symptoms of the index infection such that no additional antibacterial therapy, surgical, or radiological intervention was required. Clinical cure at the test of cure (25 to 31 days after first dose of the study drug) was assessed by non-inferiority of eravacycline to ertapenem (assessed by using the lower limit of the 95% CI for between group differences being above at least −10%). Modified intention to treat analysis (MITT), includes only the people who have taken at least 1 dose of the study drug. Micro-ITT population includes people who had baseline bacterial pathogens against at least 1 of which the study drug had in vitro antibacterial activity.

Appendix E: Literature search strategy

Database search strategies

Database: Medline

Platform: Ovid
Version: Ovid MEDLINE(R) <1946 to October 06, 2021>
Search date: 07/10/21
Number of results retrieved: 31
Search strategy:

1 eravacycline.tw. 123
2 xerava.tw. 2
3 (tp-434 or tp434).tw. 11
4 tetraphase.tw. 3
5 or/1-4 129
6 exp Intraabdominal Infections/ 47901
7 ("intra abdominal*" or intra-abdominal* or intraabdominal*).tw. 27429
8 (abdomen* adj infection*).tw. 5
9 (IAI* or cIAI*).tw. 1314
10 (peritonitis or "peritoneal inflammation" or appendicitis or diverticulitis or typhlitis or "small bowel infection*" or "abdominal sepsis" or cholecystitis or cholangitis or pancreatitis).tw. 128367
11 or/6-10 167257
12 11 and 5 34
13 limit 12 to english language 34
14 animals/ not humans/ 4861524
15 13 not 14 32
16 limit 15 to (letter or historical article or comment or editorial or news or case reports) 1
17 15 not 16 31

Database: Medline in-process

Platform: Ovid
Version: Ovid MEDLINE(R) In-Process & In-Data-Review Citations <1946 to October 06, 2021>
Search date: 07/10/21
Number of results retrieved:
Search strategy:

1 eravacycline.tw. 12
2 xerava.tw. 0
3 (tp-434 or tp434).tw. 0
4 tetraphase.tw. 0
5 or/1-4 12
6 exp Intraabdominal Infections/ 0
7 ("intra abdominal*" or intra-abdominal* or intraabdominal*).tw. 276

8 (abdomen* adj infection*).tw. 0
9 (IAI* or cIAI*).tw. 42
10 (peritonitis or "peritoneal inflammation" or appendicitis or diverticulitis or typhlitis or "small bowel infection*" or "abdominal sepsis" or cholecystitis or cholangitis or pancreatitis).tw. 1407
11 or/6-10 1668
12 11 and 5 1
13 limit 12 to english language 1

Database: Medline epubs ahead of print

Platform: Ovid
Version: Ovid MEDLINE(R) Epub Ahead of Print <October 06, 2021>
Search date: 07/10/21
Number of results retrieved: 2
Search strategy:
1 eravacycline.tw. 9
2 xerava.tw. 0
3 (tp-434 or tp434).tw. 0
4 tetraphase.tw. 0
5 or/1-4 9
6 exp Intraabdominal Infections/ 0
7 ("intra abdominal*" or intra-abdominal* or intraabdominal*).tw. 394
8 (abdomen* adj infection*).tw. 0
9 (IAI* or cIAI*).tw. 40
10 (peritonitis or "peritoneal inflammation" or appendicitis or diverticulitis or typhlitis or "small bowel infection*" or "abdominal sepsis" or cholecystitis or cholangitis or pancreatitis).tw. 1586
11 or/6-10 1968
12 11 and 5 2
13 limit 12 to english language 2

Database: Medline daily update

Platform: Ovid
Version: Ovid MEDLINE(R) Daily Update <October 06, 2021>
Search date: 07/10/21
Number of results retrieved: 1
Search strategy
1 eravacycline.tw. 1
2 xerava.tw. 0
3 (tp-434 or tp434).tw. 0
4 tetraphase.tw. 0
5 or/1-4 1

Database: Embase

Platform: Ovid
Version: Embase <1974 to 2021 October 06>

Search date:
Number of results retrieved:
Search strategy:

1	eravacycline/	435
2	eravacycline.tw.	221
3	xerava.tw.	24
4	(tp-434 or tp434).tw.	57
5	tetraphase.tw.	64
6	or/1-5	504
7	exp abdominal infection/	29584
8	("intra abdominal*" or intra-abdominal* or intraabdominal*).tw.	43434
9	(abdomen* adj infection*).tw.	13
10	(IAI* or cIAI*).tw.	2552
11	(peritonitis or "peritoneal inflammation" or appendicitis or diverticulitis or typhlitis or "small bowel infection*" or "abdominal sepsis" or cholecystitis or cholangitis or pancreatitis).tw.	192607
12	or/7-11	246222
13	12 and 6	119
14	limit 13 to english language	116
15	nonhuman/ not (human/ and nonhuman/)	4867513
16	14 not 15	103
17	16 not (letter or editorial).pt.	100

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley
Version:
CDSR –Issue 10 of 12, October 2021
CENTRAL – Issue 10 of 12, October 2021
Search date: 07/10/21
Number of results retrieved: CDSR 0 ; CENTRAL 18 .

#1	eravacycline:ti,ab	26
#2	xerava:ti,ab	0
#3	(tp-434 or tp434):ti,ab	4
#4	tetraphase:ti,ab	3
#5	{or #1-#4}	30
#6	[mh "Intraabdominal Infections"]	1074
#7	("intra abdominal*" or intra-abdominal* or intraabdominal*):ti,ab	2681
#8	(abdomen* NEAR infection*):ti,ab	42
#9	(IAI* or cIAI*):ti,ab	1094
#10	(peritonitis or "peritoneal inflammation" or appendicitis or diverticulitis or typhlitis or "small bowel infection*" or "abdominal sepsis" or cholecystitis or cholangitis or pancreatitis):ti,ab	9497
#11	{or #6-#10}	12826
#12	#11 and #5	18
#13	#12 in Cochrane Reviews	0
#14	#12 in Trials	18

Database: INAHTA database

Website: https://database.inahta.org/
Search date: 07/10/21
Number of results retrieved: 3
Search strategy:

5	#4 OR #3 OR #2 OR #1		3
4	tetraphase	0	
3	tp-434 or tp434	3	
2	xerava	0	
1	eravacycline	0	

Appendix F: Excluded studies

Study reference	Reason for exclusion
Alosaimy S, Morrisette T, Lagnf A M. et al. (2020) Real-world, multicenter experience with eravacycline for various infections. Open Forum Infectious Diseases 7(suppl1): 787	Comparator in study does not match that specified in protocol Not a relevant study design
Asempa T E., Lawrence K, Nicolau D P. et al. (2020) Efficacy and Safety of Eravacycline in Obese Patients: A Post Hoc Analysis of Pooled Data from the IGNITE1 and IGNITE4 Clinical Trials. Open Forum Infectious Diseases 7(12): 1-7	Population used in primary analysis Not a subgroup of interest Similar cure rates amongst all BMIs – does not add new information
Carr A, El Ghali A, Kaur P et al. (2020) Early real-world evidence in the use of eravacycline for the management of draconian infections. Open Forum Infectious Diseases 7(suppl1): 651-s652	Conference abstract
ChiCTR1900022060 (2019) A Phase 3, Randomized, Multicenter, Double-Blind, Double-Dummy, Parallel-Group, Comparative Study to Assess the Efficacy, Safety and Tolerability of Eravacycline Versus Ertapenem in the Treatment of Complicated Intra-Abdominal Infections (cIAI) in Hospitalized Adults. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR1900022060	Full text paper not available
Ditch K, Lawrence K, Izmailyan, S et al. (2019) Eravacycline is effective in highrisk complicated intra-abdominal infection subgroups. Critical Care Medicine 47(1supplement1)	Conference abstract
Efimova E, Tsai L, Olesky M et al. (2018) Pooled analysis of safety data from phases 2 and 3 clinical trials evaluating eravacycline in complicated intra-abdominal infections. Open Forum Infectious Diseases 5(supplement1): 573-s574	Conference abstract
Eljaaly K (2020) Efficacy and safety of eravacycline: A systematic review and meta-analysis. JACCP Journal of the American College of Clinical Pharmacy 3(8): 1685	Conference abstract
Eljaaly K, Ortwine J, K, Shaikhomer M et al. (2021) Efficacy and safety of eravacycline: A meta-analysis. Journal of global antimicrobial resistance 24: 424-428	Study does not contain a relevant intervention
Felice V, Efimova E, Izmailyan S et al. (2021) Efficacy and Tolerability of Eravacycline in Bacteremic Patients with Complicated Intra-Abdominal Infection: A Pooled Analysis from the IGNITE1 and IGNITE4 Studies. Surgical Infections 22(5): 556-561	Not prioritised, not best available evidence Subset of patients only
Fonte A, Lawrence K, Izmailyan S et al. (2018) Efficacy of eravacycline in obese patients: Pooled analysis of IGNITE1 and IGNITE4. JACCP Journal of the American College of Clinical Pharmacy 1(2): 291	Conference abstract
Fonte A, Lawrence K, Izmailyan S et al. (2018) Effect of renal function on efficacy of eravacycline: Pooled analysis of IGNITE1 and IGNITE4. JACCP Journal of the American College of Clinical Pharmacy 1(2): 290-291	Conference abstract
Hoffman-Roberts H, Scoble P, Marsh A et al. (2016) A pooled, post-hoc evaluation of the length of antibiotic therapy from IGNITE1: A phase 3 study of eravacycline (ERV) and ertapenem (ETP) for complicated intra-abdominal infections (CIAI). Surgical Infections 17(supplement1): 24	Conference abstract

Study reference	Reason for exclusion
Lan S, Chang S, Lai C et al. (2019) The efficacy and safety of eravacycline in the treatment of complicated intra-abdominal infections: A systemic review and meta-analysis of randomized controlled trials. Journal of Clinical Medicine 8(6): 866	Study does not contain a relevant intervention Phase 2 trial included
Lawrence K, Olesky M, Izmailyan S et al. (2018) Efcacy of eravacycline in secondary bacteremia: A post hoc analysis of two phase 3 studies of complicated intra-abdominal infection. Open Forum Infectious Diseases 5(supplement1): 574	Conference abstract
Newman J, Izmailyan S, Fyfe C et al. (2018) Combined microbiological response rates from two phase 3 trials demonstrating the activity of eravacycline in the treatment of complicated intra-abdominal infections: A pooled analysis of IGNITE1 and IGNITE4. Open Forum Infectious Diseases 5(supplement1): 568-s569	Conference abstract
Van H, Nicholas P, Russell M, Skorodin, Nathan C. et al. (2020) A Real-World Assessment of Clinical Outcomes and Safety of Eravacycline: A Novel Fluorocycline. Infectious Diseases and Therapy 9(4): 1017-1028	Comparator in study does not match that specified in protocol