Flomoxef

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 > 6.2.2. Watch group antibiotics

EMLc | ATC codes: J01DC14

Indication	Other specified other antibiotic resistant Enterobacterales ICD11 code: MG50.CY
INN	Flomoxef
Medicine type	Chemical agent
Antibiotic groups	WATCH
List type	Core
Formulations	**Parenteral > General injections > IV:** 0.5 g in vial powder for injection ; 1 g in vial powder for injection
EML status history	Application rejected in 2023 (TRS 1049)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Flomoxef
DrugBank	Flomoxef

Expert Committee recommendation

The Committee noted that while the available in vitro studies demonstrate that flomoxef sodium has activity against most strains of ESBL-producing Enterobacterales, validated clinical breakpoints for susceptibility testing were not currently available. The Committee also noted that most clinical trials of flomoxef sodium were performed before the emergence of ESBL-producing Enterobacterales as a common pathogen, and that evidence for the efficacy of flomoxef sodium in severe infections, where it may be of greatest value, was limited. The Committee also considered that clinical evidence for flomoxef sodium in comparison with other potentially carbapenem-sparing antibiotics in the treatment of infections caused by ESBL-producing Enterobacterales was not available. The Committee also noted that real-life experience of effective and safe use of flomoxef sodium was considerable, albeit limited to few countries in Asia. Furthermore, the Committee noted that the current market availability of flomoxef sodium was similarly limited to a small number of Asian countries. Because of these limitations, the Expert Committee considered the evidence for flomoxef sodium was uncertain, and therefore did not recommend its inclusion on the EML and EMLc for empiric treatment of community-acquired mild/moderate intra-abdominal and upper urinary tract infections caused by ESBL-producing Enterobacterales. However, the Committee acknowledged the need for effective carbapenem-sparing treatments for infections caused by ESBL-producing Enterobacterales, especially in settings where the pathogen is highly prevalent. Given this need, the

Committee considered that future evaluation of flomoxef sodium may be worthwhile once more data are available, including those from the ongoing trial in neonatal sepsis.

Background

Flomoxef sodium has not been previously considered for inclusion on the EML. It has been classified as a watch group antibiotic under the AWaRe (Access, Watch, Reserve) classification. Flomoxef sodium is an oxacephem antibiotic belonging to the oxacephem subclass of second-generation cephalosporins that are not inactivated by ESBL and narrow spectrum β-lactamases. However, flomoxef sodium is inactivated by carbapenemases and class C β-lactamases (AmpC). It has good activity against Gram-positive (except Enterococcus spp.) and Gram-negative bacteria (except Pseudomonas aeruginosa, Acinetobacter and Enterobacterales producing AmpC) and against anaerobes.

Public health relevance

There is currently no efficacious and safe alternative to the use of carbapenems for patients who are not severely ill but need treatment for intra-abdominal infections and upper urinary tract infections caused by ESBL-producing Enterobacterales, which are often quinolone resistant. However, overuse of carbapenems has caused increasing levels of carbapenem resistance, especially in pathogens that are transmitted in hospitals, increasing the urgency for alternative carbapenem-sparing options especially for non-severe infections. Cephamycins have been identified as potential definitive treatments of non-severe urinary tract infections caused by ESBL-producing Enterobacterales in a recent systematic review (1) and in two narrative reviews on this topic (2,3).

Benefits

Flomoxef sodium was first approved in 1988, based on clinical studies that were conducted between 1983 and 1988. Given the age of the antibiotic and the old pivotal trials that were conducted with different standards of rigor, the applicants compiled the evidence of efficacy based on a combination of in vitro susceptibility studies, clinical trials literature review and recommendations in guidelines. In-vitro studies The application reported the main findings of 14 studies (mostly conducted in Asia) that assessed the in vitro activity of flomoxef sodium against clinical isolates (4–17). They demonstrated a wide range of species susceptible to flomoxef sodium, both Gram-positive and Gram-negative organisms, including ESBL-producing Enterobacterales (especially the enzymes from the CTX-M group). However, flomoxef sodium did not exhibit antibacterial activity against Enterobacterales with inducible chromosomal AmpC (e.g. Enterobacter cloacae, Serratia marcescens and Citrobacter freundii) and it was inhibited by carbapenemases. It was also not active against Enterococcus spp., Pseudomonas spp. and Acinetobacter spp. The application stated that based on these in vitro studies, flomoxef displays potentially better activity than both third- and fourth-generation cephalosporins and piperacillin-tazobactam" and that flomoxef activity is inferior to the activity of all carbapenems. In vitro susceptibility studies conducted by GARDP In 2018, susceptibility to flomoxef sodium was evaluated and compared with meropenem in 40 Enterobacterales from the International Health Management Associates repository (collected from worldwide locations between 2013 and 2016) (18). Flomoxef sodium showed potent activity against the 26 ESBL-producing Enterobacterales, with a minimum inhibitory concentration (MIC) to inhibit growth of 50% of organisms (MIC50) at 0.06/0.12 mg/L, and an MIC to inhibit growth of 90% of organisms (MIC90) at 8 mg/L but it was inactive against the three carbapenem-resistant Klebsiella pneumoniae and AmpC producers. A second study tested flomoxef sodium on about 1000 Enterobacterales isolates collected between 2019 and 2021, of which 80% were resistant to third-generation cephalosporins – (70% of these were ESBL producers (19). Susceptibility to flomoxef sodium was observed in 816 isolates (82%). In comparison, susceptibility to cefuroxime was 17%, susceptibility to ceftazidime 21% and susceptibility to piperacillin-tazobactam 41%. Amikacin and fosfomycin also exhibited potent activity against the isolates of the panel, with 90% of them being susceptible. Resistance to flomoxef sodium was mainly due to AmpC and/or carbapenemase expression, although 17 (2%) ESBL-producing isolates were resistant to flomoxef sodium. Data from preapproval studies and postmarketing use Data were derived from the interview form version 11 (February 2022) (20) which, in Japan, the market authorization holder is required to provide to complement the information in the package insert. Data from preapproval studies were pooled, about 1500 patients including all

indications. For urinary tract infections the pooled cure rate was 63.0% and for acute prostatitis 95.0%. For intra-abdominal infections (peritonitis and intra-abdominal abscess), the pooled cure rate was 81.6% (71.8% for cholecystitis and cholangitis). Data from postmarketing use included almost 25 000 patients. Reported pooled cure rates were 84.2% for upper urinary tract infections and 89.5% for prostatitis/urethritis. For intra-abdominal infections (peritonitis and intra-abdominal abscess), pooled cure rates were 84.6% (83.4% for cholecystitis and cholangitis) and 91.3% in children. Cure rates were lower for severe compared to mild infections (67.9% versus 84.6% for urinary tract infections, 76.4% versus 87.2% for intra-abdominal infections) and for bloodstream/systemic infections (44.8% cure rates for severe systemic infections versus 78.7% for mild systemic infections). Systematic review GARDP conducted a systematic literature review for the purpose of the application, with the primary objective of identifying clinical efficacy and safety data for flomoxef sodium in adults, children and neonates. They included 37 studies from English databases and 176 from a Japanese database. Most studies were published before 2000, were uncontrolled and included patients with multiple sources of infection within the same study. A meta-analysis could therefore not be performed due to the low quality of studies. However, the applicants performed a targeted analysis of the subset of studies focused on intra-abdominal and urinary tract infections. Results were presented by type of infection. Intra-abdominal infections Eight studies (one randomized controlled trial, four single-arm trials and three observational studies) were identified. The randomized, double-blind, multicentre trial compared flomoxef sodium (1 g every 12 hours for 10 days) with cefotiam (1 g every 12 hours for 10 days) in 296 patients aged 16 years and older with postoperative infections (21). This was one of the pivotal trials that led to the approval of the medicine in Japan. As the trial was conducted in the 1987, no patients had intra-abdominal infections caused by ESBL-producing Enterobacterales. The per-protocol analysis included 253 evaluable patients. The clinical cure rate in the overall population was 71.4% (90/126; 95% confidence interval (CI) 63.5% to 79.3%) for flomoxef sodium and 62.2% (79/127; 95% CI 53.8% to 70.6%) for cefotiam, with no statistically significant difference. Of note, in patients with postoperative infections of the abdominal cavity and retroperitoneal space, the cure rate was significantly higher for flomoxef sodium (67.3% (37/55); 95% CI 54.9% to 79.7%) than for cefotiam (49.2% (30/61); 95% CI 36.6% to 61.7%). Results from observational studies of flomoxef sodium for the treatment of postsurgical intra-abdominal infections reported high cure rates of > 90% (22–24). A single-arm study, including only patients with biliary tract infections, reported an overall cure rate of 77.8%. The cure rate was higher for the cholecystitis subgroup (90.0%) but lower for the cholangitis subgroup (70.6%) (25). Two other single-arm studies in women reported overall cure rates of 89.4% and 90.5% for pelvic infections treated with flomoxef sodium (26,27). Urinary tract infections Sixteen studies (one randomized controlled trial, three single-arm trials and 12 observational studies) were identified. The randomized controlled trial was a double-blind, multicentre trial in adults with complicated urinary tract infections where flomoxef sodium (1 g given every 12 hours for 5 days) was compared with latamoxef (1 g given every 12 hours for 5 days) (28). The primary outcome was clinical cure. Clinical response was rated on a three-point scale (excellent, moderate or poor) based on the presence or absence of pyuria and/or bacteriuria at day 5 or end of treatment. The clinical cure rate was 68.2% (60/88, 95% CI 58.5% to 77.9%) for flomoxef sodium and 69.6% (78/112, 95% CI 61.1% to 78.2 %) for latamoxef when including all pathogens except P. aeruginosa. When only Escherichia coli infections were included, cure rates were higher in both groups (90.6% with flomoxef sodium versus 92.6% with latamoxef). As the trial was conducted in 1987, no infections were caused by extended-spectrum β-lactamase Enterobacterales. Of the 15 remaining uncontrolled studies, five had more than 25 patients (29–33) and showed varying clinical cure rates ranging from 50% (31) to 72% in patients with strains susceptible to flomoxef sodium (32). Ten studies included fewer than 25 patients (27,34–40) with clinical cure rates ranging from 45% to 100% with most having rates in the overall population of about 65%. The applicants noted that results of most of these observational trials were difficult to interpret as they enrolled few patients with infections in different sites and of varying severity. Bloodstream infections Five observational retrospective studies assessed the efficacy of flomoxef sodium monotherapy for the treatment of bloodstream infections caused by ESBL-producing Enterobacterales. Data for only four studies were available, three of which compared flomoxef sodium with a carbapenem, and one had no comparator (41–44). Overall, the conclusions were that the appropriateness of flomoxef sodium seems to depend on the MIC and severity of disease. One study compared flomoxef sodium (1 g given every 6 hours) with carbapenems (43). The 30-day all-cause mortality was 28.8% (95% CI 21.2% to 37.3%) in the flomoxef sodium

group and 12.8% (95% CI 9.0% to 17.6%) in the carbapenem group (P < 0.01). However, a subgroup analysis showed that with a flomoxef sodium MIC of < 1 mg/L, no statistically significant difference was seen in the 30-day all-cause mortality between the two groups (8.7% with flomoxef sodium and 6.4% with meropenem, P = 0.73). However, the difference was statistically significant for flomoxef sodium MIC levels of 2–8 mg/L (38.4% with flomoxef sodium and 15.6% with carbapenems, P < 0.01). In another study comparing flomoxef sodium with ertapenem for the treatment of adults with sepsis with a confirmed bacteraemia due to ESBL-producing Enterobacterales (42), no statistically significant difference in the 28-day all-cause mortality was observed between treatment groups – 20.7% (95% CI 11.2% to 33.4%) for flomoxef sodium and 15.4% (95% CI 10.6% to 21.4%) for ertapenem, P = 0.42). In a study comparing flomoxef sodium and ertapenem in adult patients with haemodialysis and bacteraemia due to ESBL-producing K. pneumoniae, there was a statistically significant difference in the 14-day mortality between flomoxef sodium and ertapenem (73.0% versus 47.0%, P < 0.05) (44). Efficacy in children According to the applicants, efficacy of flomoxef sodium in children is challenging to interpret as most studies are old, uncontrolled, have small sample sizes and included patients with multiple sources of infections in the same study. The application focused on the efficacy of flomoxef sodium for the treatment of urinary tract and intra-abdominal infections. Only two studies with more than 10 patients were available and reported data on the efficacy of flomoxef sodium for the treatment of urinary tract infections (45,46). In both cases, clinical cure rates were 100%, but due to the small sample sizes (13 and 10 patients, respectively), the results were difficult to interpret. No studies with more than 10 patients were available for intra-abdominal infections. The applicants concluded that, given that urinary tract and intra-abdominal infections present similarly in children and adults, extrapolation of efficacy for these indications is generally accepted by regulatory authorities. Pharmacokinetic (PK) and pharmacodynamics (PD) studies Evidence in adults comes from two recent studies. The optimal dosage for the treatment of urinary tract infections caused by ESBL-producing Enterobacterales was 1 g every 6 hours with normal renal function (taking 70% time above MIC as PK/PD index) (47). For intra-abdominal infections, PK/PD simulations showed the dosing regimens of 1 g 3–4 times a day had a bactericidal effect in all tissues (at an MIC of 1 mg/L and using 40% time above MIC as the PK/PD index (48). PK/PD data for neonates presented in the application suggest three different doses in the first month of life (20 mg/kg given every 12 hours in the first week, then every 6 to 8 hours in the second week and then 40 mg/kg given every 6 to 8 hours in the third and fourth week of life) (49). Of note, there is no MIC breakpoint available for flomoxef sodium and physicians in countries where flomoxef sodium is available are using the latamoxef or moxalactam MIC breakpoint, which is available from the Clinical and Laboratory Standards Institute but not from the European Committee on Antimicrobial Susceptibility Testing. Moxalactam is no longer in use and latamoxef is only used in Japan. The application concluded that the available evidence suggests flomoxef sodium is effective for the treatment of mild and moderate urinary tract and intra-abdominal infections. However, most evidence comes from old studies that were often not as methodologically rigorous as would be required today. Additionally, all data (including PK data) come from Asia, and it is unclear if differences may exist in different populations. Importantly, flomoxef sodium monotherapy for the indication of bloodstream/systemic infections showed lower efficacy with increasing severity, suggesting that this agent on its own may not be appropriate in cases with severe infections.

Harms

Safety data are derived both from patients exposed in clinical trials (about 3400 patients exposed before 1988) and patients exposed in the postmarketing setting (estimated 20.6 million patients based on sales data between 1988 and 2022). In general, the safety of flomoxef sodium is comparable to other cephalosporins and the incidence of adverse events in children and adults is similar. As with other cephalosporins, frail elderly patients who may have concomitant vitamin deficiencies, particularly vitamin K deficiencies, must be monitored closely for bleeding disorders when treated with flomoxef sodium. In pregnant and breastfeeding women, the safety of flomoxef sodium has not yet been established. Safety data in adults were extrapolated from the Japanese Flumarin® information sheet (50) and the Shionogi & Co. Interview Form v11 (February 2022) (20). According to these documents, the incidence of adverse reactions was 12.7% (414/3267 patients) in clinical trials and 2.9% (810/27 651) in a 6-year postmarketing observational survey. Seven types of clinically significant adverse reactions are reported, however no incidence data are available – shock/anaphylaxis, acute renal injury,

pancytopenia/agranulocytosis/thrombocytopenia/haemolytic anaemia, pseudomembranous colitis, toxic epidermal necrolysis/Stevens–Johnson syndrome, interstitial pneumonia/pulmonary infiltration with eosinophilia, and hepatic dysfunction/jaundice. The applicants hypothesize that these adverse reactions are rare events (< 0.1% of patients) based on previous versions of the Interview Form. Less than 5% of patients treated with flomoxef sodium had at least one adverse event in the nine small trials included in the systematic review performed by GARDP. Diarrhoea was reported in 1.4–4.4% of participants. Safety data in children are very limited. In the 6-year postmarketing observational survey, the incidence of adverse events was higher in infants (4.4%, 16/360) compared with older children up to 15 years (2.6% (74/2840). The incidence of adverse events tended to increase with longer treatment even though most children (97%) in the cohort were treated for < 14 days. Most adverse events were classified as gastrointestinal disorders. In the systematic review performed by GARDP, the overall incidence of adverse events in children was < 5%, with diarrhoea being the most frequent adverse event reported.

Cost / cost effectiveness

No published cost–effectiveness studies are available for flomoxef sodium. The application included a summary of available data of the wholesale prices of flomoxef sodium in some markets where it is available. Reported prices were US$ 5.16 (for 0.5 g) and US$ 10.35–10.38 (for 1 g).

WHO guidelines

Flomoxef sodium is not currently included in existing WHO guidelines.

Availability

Flomoxef sodium is off-patent and is currently available only in a small number of Asian countries. The three manufactures are all located in Asia and Shionogi & Co. has about 60% of the total market share.

Other considerations

The Global Coordination and Partnership department within the Antimicrobial Resistance division reviewed and provided comments on the application. The technical department acknowledged that flomoxef sodium could have an added role in the treatment of the indications outlined and could potentially be a viable carbapenem-sparing option for the treatment of resistant bacterial infections caused by ESBL-producing Enterobacterales, especially in settings with a high prevalence of ESBL-producing Enterobacterales. However, the technical department considered that more in vivo data were needed to support its inclusion on the Model Lists. Additionally, it was noted that flomoxef sodium may be of interest for the management of neonatal sepsis but that a determination in this regard is currently premature. However, flomoxef sodium could be considered for inclusion in the future once more data become available, including from the ongoing GARDP neonatal sepsis trials. The EML Antimicrobial Working Group reviewed the application and advised that it did not support the inclusion of flomoxef sodium for the treatment of intra-abdominal and upper urinary tract infections in adults and children at high risk of infection caused by ESBL-producing Enterobacterales on the EML and EMLc at this time. The Working Group acknowledged that flomoxef sodium is associated with some positive characteristics such as activity against most strains of ESBL-producing Enterobacterales. It therefore could be used as an alternative to carbapenems for empiric or targeted use of infections suspected or known to be caused by these organisms in certain situations. The Working Group also noted that there was considerable real-life experience of effective and safe use of this antibiotic over several decades in millions of patients in some countries in Asia. The Working Group noted, however, that: clinical data specifically for the efficacy of flomoxef sodium for the treatment of infections by ESBL-producing Enterobacterales were limited (especially for severe infections where it would be most useful); clinical trial data mostly predate the period when ESBL-producing Enterobacterales emerged as a common pathogen; clinical experience was mostly limited to a few Asian countries where the medicine is currently approved; validated clinical breakpoints for susceptibility testing were not available from the Clinical and Laboratory Standards Institute or the European Committee for Antimicrobial Susceptibility Testing; and a trial funded by the applicant studying flomoxef sodium in combination with another antibiotic for neonatal sepsis (an indication not requested

in this application) was still ongoing, with active recruitment. Furthermore, the Working Group considered that there were also other β-lactam antibiotics that could be used as carbapenem-sparing options due to their activity against ESBL-producing Enterobacterales (e.g. temocillin, cefoxitin) that have not been evaluated for addition to the Model Lists.

1. Aslan AT, Akova M. Extended spectrum β-lactamase producing enterobacteriaceae: carbapenem sparing options. Expert Rev Anti Infect Ther. 2019;17(12):969–81.
2. Karaiskos I, Giamarellou H. Carbapenem-sparing strategies for ESBL Producers: when and how. Antibiotics (Basel) . 2020;9(2):61.
3. Gutierrez-Gutierrez B, Rodriguez-Bano J. Current options for the treatment of infections due to extended-spectru m beta-lactamase-producing Enterobacteriaceae in different groups of patients. Clin Microbiol Infect. 2019;25(8):93 2–42.
4. Simon C, Simon M, Plieth C. In vitro activity of flomoxef in comparison to other cephalosporins. Infection. 1988;16 (2):131–4.
5. Ruckdeschel G, Eder W. Comparative in vitro activity of the new oxacephem antibiotic, flomoxef (6315-S). Eur J Cl in Microbiol Infect Dis. 1988;7(5):687–91.
6. Bauernfeind A, Schweighart S, Eberlein E, Jungwirth R. In vitro activity and stability against novel beta-lactamase s of investigational beta-lactams (cefepime, cefpirome, flomoxef, SCE2787 and piperacillin plus tazobactam) in com parison with established compounds (cefotaxime, latamoxef and piperacillin). Infection. 1991;19(Suppl 5):S264–75.
7. Cui L, Li Y, Lv Y, Xue F, Liu J. Antimicrobial resistance surveillance of flomoxef in China. J Infect Chemother. 2015; 21(5):402–4.
8. Yang Q, Zhang H, Cheng J, Xu Z, Xu Y, Cao B, et al. In vitro activity of flomoxef and comparators against Escheric hia coli, Klebsiella pneumoniae and Proteus mirabilis producing extended-spectrum beta-lactamases in China. Int J A ntimicrob Agents. 2015;45(5):485–90.
9. Yang Q, Zhang H, Cheng J, Xu Z, Hou X, Xu Y. Flomoxef showed excellent in vitro activity against clinically import ant gram-positive and gram-negative pathogens causing community- and hospital-associated infections. Diagn Micr obiol Infect Dis. 2015;81(4):269–74.
10. Sato T, Hara T, Horiyama T, Kanazawa S, Yamaguchi T, Maki H. Mechanism of resistance and antibacterial susce ptibility in extended-spectrum beta-lactamase phenotype Klebsiella pneumoniae and Klebsiella oxytoca isolated bet ween 2000 and 2010 in Japan. J Med Microbiol. 2015;64(Pt 5):538–43.
11. Matsumura Y, Yamamoto M, Nagao M, Tanaka M, Takakura S, Ichiyama S. In vitro activities and detection perfor mances of cefmetazole and flomoxef for extended-spectrum beta-lactamase and plasmid-mediated AmpC beta-lact amase-producing Enterobacteriaceae. Diagn Microbiol Infect Dis. 2016;84(4):322–7.
12. Chiu CC, Lin TC, Wu RX, Yang YS, Hsiao PJ, Lee Y, et al. Etiologies of community-onset urinary tract infections re quiring hospitalization and antimicrobial susceptibilities of causative microorganisms. J Microbiol Immunol Infect. 20 17;50(6):879–85.
13. Takesue Y, Kusachi S, Mikamo H, Sato J, Watanabe A, Kiyota H, et al. Antimicrobial susceptibility of pathogens is olated from surgical site infections in Japan: comparison of data from nationwide surveillance studies conducted in 2010 and 2014–2015. J Infect Chemother. 2017;23(6):339–48.
14. Fujita K, Takata I, Sugiyama H, Suematsu H, Yamagishi Y, Mikamo H. Antimicrobial susceptibilities of clinical isol ates of the anaerobic bacteria which can cause aspiration pneumonia. Anaerobe. 2019;57:86–9.
15. Miyazaki M, Yamada Y, Matsuo K, Komiya Y, Uchiyama M, Nagata N, et al. Change in the antimicrobial resistanc e profile of extended-spectrum beta-lactamase-producing Escherichia coli. J Clin Med Res. 2019;11(9):635–41.
16. Ngoi ST, Muhamad AN, Teh CSJ, Chong CW, Abdul Jabar K, Chai LC, et al. Beta-lactam resistance in upper respir atory tract pathogens isolated from a tertiary hospital in Malaysia. Pathogens. 2021;10(12):1062.
17. Ngoi ST, Teh CSJ, Chong CW, Abdul Jabar K, Tan SC, Yu LH, et al. In vitro efficacy of flomoxef against extended-s pectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae associated with urinary tract infectio ns in Malaysia. Antibiotics (Basel). 2021;10(2):181.
18. Activity of flomoxef against selected Enterobacteriaceae with extended-spectrum beta-lactamases and CMY (A mpC) beta-lactamases. Report study 3464-1. Monthey: IHMA Europe Sàrl; 2018.
19. Antimicrobial susceptibility testing of global clinical isolates. Report study 5158. Monthey: IHMA Europe Sàrl; 20 22.
20. [Pharmaceutical interview form 11th version for FLUMARIN® 0.5 g, 1 g and 1 g kit for intravenous injection]. Os aka: Shionogi & Co. Ltd; 2022 [Japanese].
21. Sakai K, Fujimoto M, Ueda T, Nakamura T, Hashimoto I, Sawada Y, et al. [A comparative study on the efficacy of 6315-S (flomoxef) and cefotiam against postoperative infections]. Chemotherapy. 1987;35:912-43 [Japanese].
22. Shimada M, Takenaka K, Sugimachi K. A comprehensive multi-institutional study of empiric therapy with flomox ef in surgical infections of the digestive organs. J Chemother. 1994;6(4):251–6..
23. Niwa H, Kataoka M, Kobayashi S, Yamakawa Y, Masaoka A, Hotta T, et al. [Clinical efficacy of flomoxef in surgica l infections patients. assessment of empiric therapy]. Clin Rep. 1993;27(11):4413–20 [Japanese].
24. Ota J, Taguchi T, Kawahara T, Endoh S, Tomita K, Matsunaga S, et al. [6315-S (flomoxef) in surgical infections]. Chemotherapy. 1987;35:884–95 [Japanese].
25. Tanimura H, Kobayashi N, Saito T, Huang W, Yoshida K, Takahashi H, et al. [Chemotherapy of biliary tract infecti on: tissue concentration in gallbladder, biliary excretion and clinical effects of 6315-S (flomoxef)]. Chemotherapy. 1 987;35:852–73 [Japanese].
26. Matsuda S, Okada H, Ninomiya K, Shimizu T, Noda K, Deguchi K. [Experimental and clinical studies of flomoxef i n the field of obstetrics and gynecology]. Jpn J Antibiot. 1988;41(12):1822–40 [Japanese].
27. Chimura T, Kaneko S, Haraya H, Imai T, Funaki K, Tada K, et al. [Empiric therapy of flomoxef for treatment of ob stetric-gynecological infections and the prophylaxis of postoperative infections]. Antibiot Chemother. 1992;8(2):129 –39 [Japanese].

28. Kumazawa J, Matsumoto T, Kumamoto Y, Orikasa S, Niijima T, Macheda T, et al. [6315-S (flomoxef) in complicated urinary tract infections: a double-blind controlled study using LMOX]. Chemotherapy. 1987;35:1138–63 [Japanese].
29. Goto T, Yamauchi D, Ohi Y, Kawahara K, Mizuma Y, Nakame Y, et al. [Empiric therapy with flomoxef for febrile patients with urinary tract infections]. Antibiot Chemother. 1992;8(11):2236–42 [Japanese].
30. Matsumoto T, Kitada S, Kumazawa J, Yokoo D, H. I, Ikeda M, et al. [Clinical experience with 6315-S (flomoxef) in urinary tract infection]. Chemotherapy. 1987;35:1102–21 [Japanese].
31. Kobayashi N, Yoshida K, Saitoh H, Negishi T, Yamada T, Kageyama Y, et al. [Clinical efficacy of flomoxef (FMOX) on patients with complicated urinary tract infections and patients with acute bacterial prostatitis]. Clin Rep. 1990;24(8):4121–9 [Japanese].
32. Mizuno A, Kishi M, Miyata K, Kumon H, Ohmori H, Kondo K, et al. [6315-S (Flomoxef) in complicated urinary tract infections]. Chemotherapy. 1987;35:1070–83 [Japanese].
33. Ohta N, Sudoko H, Fukuta K, Nakano M, Ushiyama T, Tajima A, et al. [Clinical trials of flomoxef in complicated urinary tract infections]. Jpn J Antibiot. 1987;40(10):1835–44 [Japanese].
34. Kuriyama M, Takahashi Y, Kato N, Ban Y, Nishiura T, Hasegawa Y, et al. 6315-S (flomoxef), a newly synthesized oxacephem, in urology. Chemotherapy. 1987;35:1032–49.
35. Fujii A, Nakanishi T, Matsumoto O, Kataoka N, Sia I, Kamidono S, et al. [6315-S (flomoxef) in urinary tract infection]. Chemotherapy. 1987;35:1059–69 [Japanese].
36. Goto T, Shimada T, Kawahara M, Kawabata T, Sakamoto N, Ohi Y, et al. [6315-S (Flomoxef) in Urinary Tract Infection]. Chemotherapy. 1987;35:1130-7 [Japanese].
37. Miyake M, Okayama S, Hirose T, Saito S, Kumamoto Y, Nishio A, et al. [6315-S (Flomoxef) in complicated urinary tract infection]. Chemotherapy. 1987;35:952–67 [Japanese].
38. Sumii T, Sanda N, Seko S, Onishi Y, Nakano H, Nihira H, et al. [6315-S (flomoxef) in urology]. Chemotherapy. 1987;35:1084–93 [Japanese].
39. Suzuki K, Takanashi K, Naide Y, Ogawa T, Tamai H, Arai T. [6315-S (flomoxef) in urological infections]. Chemotherapy. 1987;35:1016–31 [Japanese].
40. Tominaga T, Kitahara K, Kishi H, Niijima T, Ishii Y, Saitoh I, et al. [6315-S (flomoxef) in urology]. Chemotherapy. 1987;35:979–88 [Japanese].
41. Lee CH, Chen IL, Li CC, Chien CC. Relation between flomoxef minimum inhibitory concentrations and clinical outcomes of patients treated with flomoxef for Enterobacteriaceae bacteremia. Infect Drug Resist. 2018;11:2471–80.
42. Lee CH, Chen IL, Li CC, Chien CC. Clinical benefit of ertapenem compared to flomoxef for the treatment of cefotaxime-resistant Enterobacteriaceae bacteremia. Infect Drug Resist. 2018;11:257-66.
43. Lee CH, Su LH, Chen FJ, Tang YF, Li CC, Chien CC, et al. Comparative effectiveness of flomoxef versus carbapenems in the treatment of bacteraemia due to extended-spectrum beta-lactamase-producing Escherichia coli or Klebsiella pneumoniae with emphasis on minimum inhibitory concentration of flomoxef: a retrospective study. Int J Antimicrob Agents. 2015;46(6):610–5.
44. Yang CC, Wu CH, Lee CT, Liu HT, Chen JB, Chiu CH, et al. Nosocomial extended-spectrum beta-lactamase-producing Klebsiella pneumoniae bacteremia in hemodialysis patients and the implications for antibiotic therapy. Int J Infect Dis. 2014;28:3–7.
45. Fujii R, Fujita K, Murono K, Saijo M, Kakuya F, Yoshioko H, et al. [Pharmacokinetics and clinical studies on Flomoxef in neonates and premature infants]. Jpn J Antibiot. 1993;46(7):518–38 [Japanese].
46. Motohiro T, Oda K, Aramaki M, Kawakami A, Tanaka K, Koga T, et al. [Pharmacokinetics and clinical studies of flomoxef in the paediatric field]. Jpn J Antibiot. 1987;40(8):1515-34 [Japanese].
47. Hamada Y, Kasai H, Suzuki-Ito M, Matsumura Y, Doi Y, Hayakawa K. Pharmacokinetic/pharmacodynamic analysis and dose optimization of cefmetazole and flomoxef against extended-spectrum beta-lactamase-producing Enterobacterales in patients with invasive urinary tract infection considering renal function. Antibiotics (Basel). 2022;11(4):456.
48. Hirano T, Ohge H, Ikawa K, Uegami S, Watadani Y, Shigemoto N, et al. Pharmacokinetics of flomoxef in plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue of patients undergoing lower gastrointestinal surgery: dosing considerations based on site-specific pharmacodynamic target attainment. J Infect Chemother. 2023;29(2):186–92.
49. Darlow CA, Hope W. Flomoxef for neonates: extending options for treatment of neonatal sepsis caused by ESBL-producing Enterobacterales. J Antimicrob Chemother. 2022;77(3):711–8.
50. [Japanese Pharmacopoeia (product information sheet) for FLUMARIN® for intravenous injection]. Osaka: Shionogi & Co. Ltd; 2022 [Japanese].

