

Drug Class Update with New Drug Evaluation: Fluoroquinolones

Date of Review: March 2018
Generic Name: delafloxacin

End Date of Literature Search: 12/30/2017
Brand Name (Manufacturer): Baxdela™
Dossier Received: yes

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:

The purpose of this class update is to review new comparative evidence for efficacy and safety of oral fluoroquinolones (FQs) and to evaluate the evidence and place in therapy of the recently approved fluoroquinolone, delafloxacin.

Research Questions:

1. Is there new comparative evidence that oral fluoroquinolones differ in efficacy/effectiveness in the clinical cure of acute bacterial infections?
2. Is there new comparative evidence that oral FQs differ in serious adverse events or tolerability when used to manage acute bacterial infections?
3. Are there specific subpopulations for which one oral fluoroquinolone is more effective or better tolerated than other FQs?

Conclusions:

- There is no new moderate or high-quality comparative evidence that suggests of a difference in effectiveness of FQs to susceptible bacterial pathogens.
- There is insufficient evidence to determine if one FQ antibiotic is more effective or safer than other antibiotics in the treatment of diabetic foot infections.
- FQs should be reserved for serious infections requiring broad-spectrum coverage. Due to potential side effects (tendinitis and tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy, and central nervous system), FQs should be avoided as first-line treatment for uncomplicated infections.
- There is low quality evidence that delafloxacin is noninferior to vancomycin plus aztreonam in clinical response of acute bacterial skin and skin structure infections (ABSSSIs) based on two noninferior trials with high risk of bias and low applicability.

Recommendations:

- Continue to maintain at least one FQ with broad coverage of gram-negative bacteria and at least one 'respiratory' FQ as preferred options.
- Review comparative drug costs in executive session.

Previous Conclusions:

- Moderate quality evidence continues to support previous conclusions that there is no difference in effectiveness of fluoroquinolones (FQs) to susceptible bacteria.
- Low quality evidence suggests there may be some differences in harms between FQs. In particular, ofloxacin may be associated with highest risk of tendon injury while levofloxacin may be associated with least risk. Levofloxacin may be associated with higher risk of hyperglycemia or hypoglycemia and moxifloxacin may be associated with no risk for dysglycemia. Ciprofloxacin and levofloxacin appear to have little risk for QT-interval prolongation relative to other FQs. Levofloxacin may be associated with the least risk for neurotoxicity-related adverse events. All FQs are associated with *Clostridium difficile* infection and there does not appear to be any differences in risk among this class.

Previous Recommendations:

- Continue to maintain at least one FQ with broad coverage of gram-negative bacteria (ciprofloxacin, levofloxacin) and at least one “respiratory” third-generation FQ (gemifloxacin, levofloxacin, moxifloxacin).

Background:

Fluoroquinolones antibiotics interfere with bacterial DNA synthesis by inhibiting topoisomerase II (DNA gyrase) in gram-negative organisms and topoisomerase IV in gram-positive organisms.¹ Fluoroquinolones are bactericidal and exhibit post-antibiotic effects of inhibition of bacterial growth even after the plasma concentration falls below the minimum inhibitory concentration (MIC). They have good oral bioavailability and penetrate most body tissues. Other than moxifloxacin, the FQs are eliminated through the kidneys via active tubular secretion.¹ FQs have a broad spectrum of activity, including against *Pseudomonas aeruginosa* and *Staphylococci*. FQs are classified by generation based on their antimicrobial spectrum of activity and intended use (Table 1). Due to the broad-spectrum activity of FQs, there is widespread incentive to preserve the efficacy of these drugs by reserving them as second-line when narrow-spectrum antibiotics can be utilized first. Resistance to FQs is also increasing rapidly and is considered a major concern in the clinical setting.²

Table 1: Characteristics of Fluoroquinolones by Generation³

Generation	Agents	Spectrum of Activity	Indications
First Generation	Nalidixic acid	<i>Enterobacteriaceae</i>	Not used for systemic infections, uncomplicated UTI only
Second Generation	Norfloxacin, ofloxacin, ciprofloxacin	<i>Enterobacteriaceae</i> , atypical pathogens, <i>P. aeruginosa</i> (Cipro only), <i>Pneumococci</i>	UTI, gastroenteritis, prostatitis, nosocomial infections, STDs
Third Generation	Levofloxacin	<i>Enterobacteriaceae</i> , atypical pathogens, <i>Streptococci</i> , <i>Pneumococci</i>	UTI, gastroenteritis, prostatitis, nosocomial infections, STDs, community acquired pneumonia
Fourth Generation	Moxifloxacin, gemifloxacin	<i>Enterobacteriaceae</i> , <i>P. aeruginosa</i> , atypical pathogens, MSSA, <i>Streptococci</i> , anaerobes, <i>Pneumococci</i>	UTI, gastroenteritis, prostatitis, nosocomial infections, STDs, community acquired pneumonia, intra-abdominal infections

Abbreviations: MSSA = methicillin-susceptible *Staphylococcus aureus*; UTI: urinary tract infection; STD: sexually transmitted disease

Delafloxacin is a recently approved FQ, which has shown good *in vitro* and *in vivo* activity against major pathogens associated with community acquired pneumonia (CAP) and acute bacterial skin and skin structure infections (ABSSSI). It has been studied in both infections, but is currently only approved for ABSSSI.⁴ It also shows good activity against a broad spectrum of microorganisms, including Gram-positive, Gram-negative, atypical and anaerobic organisms. Delafloxacin is the first FQ with activity against methicillin resistant *Staphylococcus aureus* (MRSA). It is available in oral and intravenous (IV) formulations.

ABSSSIs are classified as simple or complicated, purulent or nonpurulent, and can involve the skin, subcutaneous fat, fascial layers and musculotendinous tissues.⁵ Current guidelines from the Infectious Disease Society of America (IDSA) recommend treatment with antibiotics based on severity, location, presence of purulence, and degree of systemic signs of infection.⁶ While most community-acquired cases are caused by *S. aureus* and *Streptococci*, gram negative bacteria (*Enterococcus*, *E. coli*, *P. aeruginosa*) are often localized from diabetic lower limb infections and necrotizing infections which can be polymicrobial and involve anaerobes. In the IDSA guidelines, FQs are specifically recommended for the following: 1) in combination with metronidazole for surgical site infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract; and 2) treatment of necrotizing infection of the skin, fascia and muscle.⁶ In less severe skin and soft tissue infections (SSTI), narrow-spectrum agents are recommended to target appropriate bacterial pathogens.

The FDA guidance defines ABSSSI types that can be enrolled in ABSSSI trials as a bacterial infection of the skin with a lesion size of at least 75 cm² and includes cellulitis/erysipelas, wound infection, and major cutaneous abscess.⁷ The ABSSSI indications excludes deeper infections such as necrotizing infections, ulcerations and diabetic foot infections. Outcomes of interest in the treatment of ABSSSI include ABSSSI-related mortality, clinical cure (resolution of symptoms and signs) and microbiological cure, or eradication of bacteria.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. Low quality evidence will only be highlighted if moderate- to high-quality evidence is unavailable.

Systematic Reviews:

A systematic review from Cochrane Collaboration was performed to determine the efficacy and safety of systemic antibiotics in the treatment of diabetic foot infections.⁸ It is unknown whether one antibiotic treatment, including FQs, is more effective or safer than another antibiotic regimen for the treatment of diabetic foot infections due to heterogeneous data of clinical trials with unclear or high risk of bias due to industry funding, unclear allocation concealment, and high risk of detection bias.

Two additional systematic reviews^{9,10} were identified and excluded due to poor quality evidence, high heterogeneity, and wrong study design of trials included. In one of these reviews, the investigators found the data insufficient to make strong conclusions on the absolute risk of arrhythmias with FQs.¹⁰

New Guidelines:

The Infectious Disease Society of America (IDSA) and American Thoracic Society published a clinical practice guideline on the management of adults with hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) in 2016.¹¹ The guideline panel required conflict of interest (COI) disclosures and had an adequate management plan for COI. Panelists were categorized as cleared for full participation, allowed to participate with recusal for certain aspects, or disqualified from participation. The co-chairs remained free of any financial COI.

Fluoroquinolones are recommended in the following instances:

- Levofloxacin is recommended as a treatment option for empiric treatment of VAP and HAP when coverage for methicillin-susceptible *Staphylococcus aureus* (MSSA) is indicated (weak recommendation, very low-quality evidence) noting that FQ resistance is slightly more common in MSSA versus other treatment options. Therapy should be narrowed once a bacterial pathogen has been isolated.

New Formulations or Indications:

None identified.

New FDA Safety Alerts:

In May 2016, the FDA issued new safety warnings regarding the risk of adverse effects including tendinitis and tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy, and central nervous system effects with FQs.¹² The FDA advised FQs be reserved for uncomplicated infections (sinusitis, bronchitis, and uncomplicated urinary tract infections) for which the risk of these adverse events outweighs the benefit. A boxed warning was added to drug labeling for FQs.

In May 2017, FDA confirmed that current data do not support reports that FQs may cause retinal detachment, aortic aneurysm or aortic dissection.¹²

Randomized Controlled Trials:

A total of 25 citations were manually reviewed from the initial literature search. After further review, 24 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Postma, et al. ¹³ Cluster, RCT, non-inferiority	Beta-lactam monotherapy (BL) vs. Beta-lactam + macrolide (BL/MC) vs. FQ monotherapy	Hospitalized adults with CAP (n=2283)	All-cause mortality within 90 days of admission	<u>All-cause 90 day mortality</u> BL: 59 (9.0%) BL/MC: 82 (11.1%) FQ: 78 (8.8%) <i>BL vs. BL/MC: Treatment difference 1.9% (90% CI -0.6 to 4.4)</i>

				<i>BL vs. FQ: Treatment difference 0.6% (90% CI -2.8 to 1.9)</i>
Abbreviations: BL: Beta-lactam; CAP: community acquired pneumonia; FQ: fluoroquinolone; MC: macrolide; RCT: randomized controlled trial				

NEW DRUG EVALUATION: Baxdela® (delafloxacin)

Delafloxacin is a FQ antibiotic indicated for adults for the treatment of ABSSSI caused by susceptible bacteria. See **Appendix 4 for Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Prior phase 2 studies showed that delafloxacin is well tolerated and has similar clinical efficacy compared with tigecycline, linezolid and vancomycin.^{14,15} A post-hoc analysis demonstrated superior clinical success rates in obese patients with delafloxacin compared to vancomycin in one Phase 2 study which led to an enrichment of the following phase 3 trials with subjects with BMIs ≥ 30 .⁷

Delafloxacin was approved based on two Phase 3, multicenter, randomized, double-blind, noninferiority trials with high risk of bias comparing delafloxacin to vancomycin plus aztreonam in the treatment of moderate to severe ABSSSI. Only one of these trials is currently published and can be fully assessed for quality.¹⁶ Both studies were similarly designed with the key difference being study 302 included delafloxacin IV only and study 303 included IV to oral switch. Inclusion and exclusion criteria were almost identical except study 302 excluded patients with a creatinine clearance (CrCl) < 30 mL/min and body weight > 140 kg, while 303 excluded those with CrCl < 15 mL/min and body weight > 200 kg. Specific inclusion and exclusion criteria are included in the evidence table below. The key characteristics of the two studies were consistent with the recommendations in the FDA guidance on ABSSSI studies including infection type, lesion size, use of prior ineffective antibacterial drugs, and endpoints.⁸ The primary outcome in both studies was clinical response defined as $\geq 20\%$ reduction in erythema of the ABSSSI lesion at 48-72 hours. The FDA guidance defined non-inferiority acceptable if the lower limit of the 95% CI was greater than -10%.

In the published noninferiority study (study 302) with high risk of bias, 331 patients were randomized to IV delafloxacin and 329 patients were randomized to IV vancomycin plus aztreonam. Patients in this trial had the following infections: cellulitis (39%), wound infection (35%), major cutaneous abscess (25%), and burn infection (1%). Patients continued on IV therapy for the entire duration of therapy and aztreonam was discontinued once baseline cultures did not reveal gram-negative organisms. Although patients on delafloxacin received an IV placebo infusion instead of aztreonam, it is unclear how the investigators maintained blinding with variability in vancomycin dosing schedules based on trough levels. Overall, *S. aureus* was identified in approximately 66% of cases; MRSA was found in 32% of patients the delafloxacin group and 36.8% of patients in the vancomycin/aztreonam group.

Intravenous delafloxacin was found to be noninferior to IV vancomycin plus aztreonam in clinical response (78.2% vs. 80.9%; treatment difference -2.6%; 95% CI -8.78 to 3.57%) and investigator-assessed cure (52% vs. 50.5%; treatment difference 1.5%; 95% CI -6.11 to 9.11%), with the lower limit of the 95% CI greater than -10% for both outcomes.

Study 303 remains unpublished and could not be fully assessed for quality and risk of bias. Much of the information from the evidence table comes from the FDA review.⁷ In this study, 423 patients were randomized to delafloxacin and 427 patients were randomized to vancomycin plus aztreonam. This trial implemented a mandatory switch from IV delafloxacin to oral therapy after 48 hours (6 doses). The patients in the vancomycin arm were switched to an oral

placebo and IV placebo infusions were used to maintain blinding. Patients in this trial had the following infections: cellulitis (48%), wound infection (26%), major cutaneous abscess (25%), and burn infection (1%).

Consistent with the previous trial, IV to oral delafloxacin was found to be noninferior to IV vancomycin plus aztreonam for clinical response (83.7% vs. 80.6% treatment difference 3.1%; 95% CI -2.0 to 8.3%) with the lower limit of the 95% CI greater than -10% non-inferiority margin.

In both trials, approximately 90% of baseline isolates were Gram-positive organisms and over 60% were *S. aureus* (56% MSSA and 44% MRSA). Gram-negative isolates were uncommon but most were from polymicrobial infections that included Gram-positive organisms. In both trials, the microbiologic response rates by baseline organisms did not differ significantly between the delafloxacin and vancomycin/aztreonam arms (Table 2).

Table 2. Pooled Outcomes by Baseline Pathogens (MITT population)⁹

Pathogen	Clinical Response at 48-72 hours ^a		Investigator-Assessed Success at Follow-up ^b	
	Delafloxacin, n/N (%)	Comparator, n/N (%)	Delafloxacin, n/N (%)	Comparator, n/N (%)
<i>Staphylococcus aureus</i>	271/319 (85.0%)	269/324 (83.0%)	275/319 (86.2%)	269/324 (83.0%)
Methicillin-susceptible	149/177 (84.2%)	148/180 (80.9%)	154/177 (87.0%)	153/183 (83.6%)
Methicillin-resistant	125/144 (86.8%)	121/141 (85.8%)	122/144 (84.7%)	116/141 (82.3%)
<i>Streptococcus pyogenes</i>	17/23 (73.9%)	9/18 (50.0%)	21/23 (91.3%)	16/18 (88.9%)
<i>Streptococcus agalactiae</i>	10/14 (71.4%)	9/12 (75.0%)	12/14 (85.7%)	11/12 (91.7%)
<i>Escherichia coli</i>	12/14 (85.7%)	16/20 (80.0%)	12/14 (85.7%)	18/20 (90.0%)
<i>Klebsiella pneumoniae</i>	19/22 (86.4%)	22/23 (95.7%)	20/22 (90.9%)	21/23 (91.3%)
<i>Pseudomonas aeruginosa</i>	9/11 (81.8%)	11/12 (91.7%)	11/11 (100.0%)	12/12 (100.0%)

^a Objective clinical response was defined as 20% or greater decrease in lesion size as determined by digital planimetry of the leading edge of erythema at 48 to 72 hours after initiation of treatment.

^b Investigator-assessed success was defined as complete or near resolution of signs and symptoms, with no further antibacterial needed at Follow-up Visit (Day 14±1).

Applicability of these studies is low since exclusion criteria was extensive and included many comorbidities commonly seen in patients at risk for ABSSSI (underlying skin condition, impaired arterial blood supply to extremities, peripheral neuropathy, liver disease, renal disease). In addition, less than 10% of patients in the studies had diabetes which is lower than what is seen in practice. More than 90% of pathogens identified were gram-positive organisms, mainly *Staphylococcus* and *Streptococcus* species. Thus, delafloxacin provides broad-spectrum gram-negative coverage that may not be necessary for most ABSSSIs. In the trials, cellulitis/erysipelas accounted for the majority of ABSSSI infections across most regions and countries except for the U.S. where wound infections accounted for the majority of infections. However, many of the designated wound infections resulted from the puncturing of skin with syringes in IV drug users. This is inconsistent with the definition of wound infection and it is unknown how many of these patients may have actually had an abscess.

More studies are needed to adequately assess the place in therapy of delafloxacin. There is currently an ongoing study comparing delafloxacin to moxifloxacin in patients with community acquired pneumonia.

Clinical Safety

No significant safety concerns emerged for 741 patients included in the two Phase 3 trials. The common adverse reactions reported in the clinical trials included nausea, diarrhea, headache, transaminase elevations and vomiting (table 3). There were no reports of tendinitis or tendon rupture, peripheral neuropathy or myopathy; however, post marketing data will be necessary to determine the risks associated with delafloxacin.

Table 3. Most Common Adverse Reactions Occurring in $\geq 2\%$ of Patients Receiving Delafloxacin¹⁸

Adverse Reactions	Delafloxacin, N = 741 (%)	Comparator, N = 751 (%)
Nausea	8%	6%
Diarrhea	8%	3%
Headache	3%	6%
Transaminase Elevations*	3%	4%
Vomiting	2%	2%

*include hypertransaminasemia, increased transaminases, and increased ALT and AST

Serious adverse events (SAEs) were reported by 27 (3.6%) patients in the delafloxacin arm and 16 (3.5%) patients in the comparator arm. SAEs that were reported in more than one delafloxacin-treated patient included cellulitis/erysipelas/skin infection (n=4), sepsis/septic shock (n=2) and pulmonary embolism (n=2). Discontinuation of study drug due to treatment emergent adverse events was reported in 13 (1.8%) patients in the delafloxacin arm and in 26 (3.5%) in the comparator arm.

Table 4. Pharmacology and Pharmacokinetic Properties^{7,18}

Parameter	
Mechanism of Action	Fluoroquinolone class of antibacterial drug whose antibacterial activity is due to the inhibition of both bacterial topoisomerase IV and DNA gyrase (topoisomerase II) enzymes which are required for bacterial DNA replication, transcription, repair, and recombination. It exhibits concentration-dependent bactericidal activity against gram-positive and gram-negative bacteria in vitro.
Oral Bioavailability	Bioavailability of 450 mg oral tablet administered as a single dose = 58.8%
Distribution and Protein Binding	$V_{d,ss}$ = 30 to 48 L Plasma protein binding = 84%
Elimination	Mean CL following single IV 300 mg administration = 16.3 L/h (SD 3.7 L/h) CLr = 35 to 45% of total clearance
Half-Life	Mean $t_{1/2}$ for single-dose IV administration = 3.7 hours (SD 0.7 hour) Mean $t_{1/2}$ for multiple oral administration = 4.2 to 8.5 hours
Metabolism	Primarily glucuronidation with oxidative metabolism representing 1% of administered dose;

		infection, septic arthritis, endocarditis, severely impaired arterial blood supply to extremity with ABSSSI or poor circulatory status, severely compromised immune system, liver disease, CrCl < 30 ml/min, peripheral neuropathy, > 140 kg, other severe underlying comorbidities					(diabetes, poor circulatory status, peripheral neuropathy). Significant exclusion criteria limits generalizability to real-world patients. <u>Intervention</u> : Both treatments provide broad spectrum coverage that may not be necessary for ABSSSI predominantly caused by staph and strep infections. <u>Comparator</u> : Both treatments provide broad spectrum coverage that may not be necessary for ABSSSI predominantly caused by staph and strep infections. <u>Outcomes</u> : Outcome appropriate based on FDA guidance for ABSSSI. Could be at risk for subjective variability. <u>Setting</u> : Multiple centers in seven countries, including Croatia, Israel, Latvia, Russian Federation, Spain, Ukraine, and United States. ~80% from the U.S.
2. Study 3037 Phase 3 MC, DB, NI, RCT	1. DFX 300 mg IV Q12h for 6 doses, then PO DFX 450 mg Q12h 2. VANC 15 mg/kg IV + AZT 2 g Q12h; after 6 doses, included PO placebo Duration 5-14 days, at investigator discretion	<u>Demographics</u> : Male: 63.3% White: 82.7% Mean age: 50.7 yo Mean BMI: 30.5 kg/m ² (50.0% of patients with BMI ≥30kg/m ²) <u>Key Inclusion Criteria</u> : Adult (≥18 yo) with ABSSSI, and ≥2 signs of systemic infection <u>Key Exclusion Criteria</u> : Receipt of systemic abx in the 14 days prior to enrollment with some exceptions, chronic or underlying skin condition, DFI, osteomyelitis, animal bite, necrotizing infection, septic arthritis, endocarditis, severely impaired arterial blood supply to extremity with ABSSSI or poor circulatory	<u>ITT</u> : 1. 423 2. 427 <u>Safety</u> : 1. 417 2. 425 <u>Attrition</u> : 1. 57 2. 59	<u>Primary Endpoint</u> : Clinical Response: 1. 354/423 (83.7%) 2. 344/427 (80.6%), MD 3.1% (95% CI, -2.0 to 8.3) <u>Secondary Endpoints</u> : Investigator-assessed cure at FU: 1. 244/423 (57.7%) 2. 255/427 (59.7%) MD: -2.0% (95% CI, -8.6 to 4.6) Investigator-assessed cure at LFU: 1. 287/423 (67.8%) 2. 303/427 (71.0%) MD:-3.1% (95% CI, -9.3 to 3.1)	NS NS NS	<u>DC due to AE</u> : 1. 10 2. 17 <u>Overall serious AEs</u> : 16/417 (3.8%) vs. 17/425 (4.0%)	NS NS Risk of Bias (low/high/unclear) : <u>Selection Bias</u> : UNCLEAR; unpublished. No available information on randomization and allocation concealment. Groups similar at baseline. <u>Performance Bias</u> : UNCLEAR. Double-blind, placebo infusion given in combination with DFX to maintain blinding. However, potential of vancomycin dosing variability to unblind treatment. <u>Detection Bias</u> : UNCLEAR <u>Attrition Bias</u> : HIGH. Overall attrition was 13.6% but similar between groups. (13.5% in DFX and 13.8% in VANC/AZT) <u>Reporting Bias</u> : UNCLEAR. The work was funded by Melinta Therapeutics. Applicability : <u>Patient</u> : Narrow ethnic diversity. Excludes comorbidities commonly seen in practice as risk factors for skin and soft tissue infections (diabetes, poor circulatory status, peripheral neuropathy). Significant exclusion criteria limits generalizability to real-world patients. <u>Intervention</u> : Both treatments provide broad spectrum coverage that may not be necessary for ABSSSI predominantly caused by staph and strep infections.

		status, severely compromised immune system, liver disease, CrCl < 15ml/min, peripheral neuropathy, > 200 kg, other severe underlying comorbidities						<p><u>Comparator:</u> Both treatments provide broad spectrum coverage that may not be necessary for ABSSSI predominantly caused by staph and strep infections.</p> <p><u>Outcomes:</u> Outcome appropriate based on FDA guidance for ABSSSI. Could be at risk for subjective variability.</p> <p><u>Setting:</u> Multiple centers in 16 countries in North America, Latin America, Eastern Europe, and Asia.</p>
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*Systemic signs of ABSSSI included lymph node enlargement, elevated C-reactive protein (>10x upper limit of normal), elevated white blood cell count ($\geq 10,000$ cell/ μ L), fever ($\geq 38^{\circ}\text{C}$), and lymphangitis

Abbreviations [alphabetical order]: ABSSI = acute bacterial skin and skin structure infections; ABW = actual body weight; abx = antibiotic; AE = adverse event; ARR = absolute risk reduction; AZT = aztreonam; BMI = body mass index; CI = confidence interval; combo = combination; DB = double-blind; DC = discontinuation; DD = double-dummy; DFX = delafloxacin; FU = follow-up (day 14); ITT = intention to treat; IV = intravenous; LFU = late follow-up (days 21-28); MC= multicenter; MD = mean difference; MN = multinational; MSA = minimum surface area; N = number of subjects; NA = not available; NI = noninferiority; NNH = number needed to harm; NNT = number needed to treat; PO = oral; Q12h = every 12 hours; RCT = randomized controlled trial; SA = short-acting; SD = standard deviation; SI = systemic infection; tx = therapy; VANC = vancomycin; yo = years old

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DRAFT

Appendix 1: Current Preferred Drug List

PDL	Generic	Brand	Route	Form
Y	CIPROFLOXACIN HCL	CIPRO	ORAL	TABLET
Y	CIPROFLOXACIN HCL	CIPROFLOXACIN HCL	ORAL	TABLET
Y	CIPROFLOXACIN HCL	CIPRO	ORAL	TABLET
Y	CIPROFLOXACIN HCL	CIPROFLOXACIN HCL	ORAL	TABLET
Y	CIPROFLOXACIN HCL	CIPROFLOXACIN HCL	ORAL	TABLET
Y	CIPROFLOXACIN HCL	CIPROFLOXACIN HCL	ORAL	TABLET
Y	LEVOFLOXACIN	LEVAQUIN	ORAL	TABLET
Y	LEVOFLOXACIN	LEVOFLOXACIN	ORAL	TABLET
Y	LEVOFLOXACIN	LEVAQUIN	ORAL	TABLET
Y	LEVOFLOXACIN	LEVOFLOXACIN	ORAL	TABLET
Y	LEVOFLOXACIN	LEVAQUIN	ORAL	TABLET
Y	LEVOFLOXACIN	LEVOFLOXACIN	ORAL	TABLET
Y	LEVOFLOXACIN	LEVOFLOXACIN	ORAL	SOLUTION
Y	LEVOFLOXACIN	LEVOFLOXACIN	ORAL	SOLUTION
Y	LEVOFLOXACIN	LEVOFLOXACIN	ORAL	SOLUTION
Y	CIPROFLOXACIN	CIPRO	ORAL	SUS MC REC
Y	CIPROFLOXACIN	CIPROFLOXACIN	ORAL	SUS MC REC
Y	CIPROFLOXACIN	CIPRO	ORAL	SUS MC REC
Y	CIPROFLOXACIN	CIPROFLOXACIN	ORAL	SUS MC REC
N	OFLOXACIN	OFLOXACIN	ORAL	TABLET
N	OFLOXACIN	OFLOXACIN	ORAL	TABLET
N	MOXIFLOXACIN HCL	AVELOX	ORAL	TABLET
N	MOXIFLOXACIN HCL	MOXIFLOXACIN HCL	ORAL	TABLET
N	CIPROFLOXACIN/CIPROFLOXA HCL	CIPROFLOXACIN ER	ORAL	TBMP 24HR
N	CIPROFLOXACIN/CIPROFLOXA HCL	CIPROFLOXACIN ER	ORAL	TBMP 24HR

Appendix 2: Abstracts of Comparative Clinical Trials

Postma DF, van Werkhoven CH, van Elden LJ, et al.. Antibiotic treatment strategies for community-acquired pneumonia in adults. *N Engl J Med*. 2015 Apr 2;372(14):1312-23.

BACKGROUND: The choice of empirical antibiotic treatment for patients with clinically suspected community-acquired pneumonia (CAP) who are admitted to non-intensive care unit (ICU) hospital wards is complicated by the limited availability of evidence. We compared strategies of empirical treatment (allowing deviations for medical reasons) with beta-lactam monotherapy, beta-lactam-macrolide combination therapy, or fluoroquinolone monotherapy.

METHODS: In a cluster-randomized, crossover trial with strategies rotated in 4-month periods, we tested the noninferiority of the beta-lactam strategy to the beta-lactam-macrolide and fluoroquinolone strategies with respect to 90-day mortality, in an intention-to-treat analysis, using a noninferiority margin of 3 percentage points and a two-sided 90% confidence interval.

RESULTS: A total of 656 patients were included during the beta-lactam strategy periods, 739 during the beta-lactam-macrolide strategy periods, and 888 during the fluoroquinolone strategy periods, with rates of adherence to the strategy of 93.0%, 88.0%, and 92.7%, respectively. The median age of the patients was 70 years. The crude 90-day mortality was 9.0% (59 patients), 11.1% (82 patients), and 8.8% (78 patients), respectively, during these strategy periods. In the intention-to-treat analysis, the risk of death was higher by 1.9 percentage points (90% confidence interval [CI], -0.6 to 4.4) with the beta-lactam-macrolide strategy than with the beta-lactam strategy and lower by 0.6 percentage points (90% CI, -2.8 to 1.9) with the fluoroquinolone strategy than with the beta-lactam strategy. These results indicated noninferiority of the beta-lactam strategy. The median length of hospital stay was 6 days for all strategies, and the median time to starting oral treatment was 3 days (interquartile range, 0 to 4) with the fluoroquinolone strategy and 4 days (interquartile range, 3 to 5) with the other strategies.

CONCLUSIONS: Among patients with clinically suspected CAP admitted to non-ICU wards, a strategy of preferred empirical treatment with beta-lactam monotherapy was noninferior to strategies with a beta-lactam-macrolide combination or fluoroquinolone monotherapy with regard to 90-day mortality. (Funded by the Netherlands Organization for Health Research and Development; CAP-START ClinicalTrials.gov number, [NCT01660204](#).)

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 4 2017

1 exp Fluoroquinolones/ 32406

2 exp Ciprofloxacin/ 13269

3 exp Levofloxacin/ 3115

4 exp Ofloxacin/ 7237

5 moxifloxacin.mp. 4038

6 gemifloxacin.mp. 446

7 exp Norfloxacin/ 2518

8 delafloxacin.mp. 39

9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 33539

10 limit 9 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) 380

11 Administration, Oral/ or oral.mp.

12 oral.mp*

13 11 or 12

14 10 and 13

15 from 14 keep 1-2, 4, 8, 12, 16-17, 21... 25

Appendix 4: Prescribing Information Highlights⁴

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BAXDELA™ safely and effectively. See full prescribing information for BAXDELA.

BAXDELA (delafloxacin) tablets, for oral use
BAXDELA (delafloxacin) for injection, for intravenous use
Initial U.S. Approval: 2017

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS, and EXACERBATION OF MYASTHENIA GRAVIS

See full prescribing information for complete boxed warning.

Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together (5.1), including:

- Tendinitis and tendon rupture (5.2)
- Peripheral neuropathy (5.3)
- Central nervous system effects (5.4)

Discontinue BAXDELA immediately and avoid the use of fluoroquinolones, including BAXDELA, in patients who experience any of these serious adverse reactions. (5.1)

- Fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis. Avoid BAXDELA in patients with known history of myasthenia gravis. (5.5)

-----**INDICATIONS AND USAGE**-----

BAXDELA is a fluoroquinolone antibacterial indicated in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria. (1.1)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of BAXDELA and other antibacterial drugs, BAXDELA should be used only to treat infections that are proven or strongly suspected to be caused by bacteria. (1.2)

-----**DOSAGE AND ADMINISTRATION**-----

- Administer BAXDELA for injection 300 mg by intravenous infusion over 60 minutes, every 12 hours, or a 450-mg BAXDELA tablet orally every 12 hours for 5 to 14 days total duration. (2.1)
- Dosage for patients with renal impairment is based on the estimated glomerular filtration rate (eGFR) (2.3)

Estimated Glomerular Filtration Rate (eGFR)(mL/min/1.73m ²) ^a	Recommended Dosage Regimen for BAXDELA ^c	
	Oral	Intravenous ^b
30-89	No dosage adjustment	No dosage adjustment
15-29	No dosage adjustment	200 mg every 12 hours
End Stage Renal Disease (ESRD) (<15 including hemodialysis)	Not Recommended ^d	
a. Estimate of GFR based on a Modification of Diet in Renal Disease (MDRD) equation. b. All intravenous doses of BAXDELA are administered over 60 minutes. c. For a total treatment duration of 5 to 14 days. d. Not recommended due to insufficient information to provide dosing recommendations.		

-----**DOSAGE FORMS AND STRENGTHS**-----

- For Injection: 300 mg of delafloxacin (equivalent to 433 mg delafloxacin meglumine) as a lyophilized powder in a single dose vial for reconstitution and further dilution before intravenous infusion. (3)
- Oral Tablets: 450 mg delafloxacin (equivalent to 649 mg delafloxacin meglumine). (3)

-----**CONTRAINDICATIONS**-----
 Known hypersensitivity to BAXDELA or other fluoroquinolones (4, 5.6)

-----**WARNINGS AND PRECAUTIONS**-----

- Hypersensitivity Reactions: May occur after first or subsequent doses of BAXDELA. Discontinue BAXDELA at the first sign of a skin rash or any other sign of hypersensitivity. (5.7)
- Clostridium difficile-associated diarrhea: Evaluate if diarrhea occurs. (5.8)

-----**ADVERSE REACTIONS**-----

Most common adverse reactions (incidence ≥ 2%) are nausea, diarrhea, headache, transaminase elevations and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Melinta Therapeutics at (844) 635-4682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

-----**USE IN SPECIFIC POPULATIONS**-----

Renal Impairment: Closely monitor serum creatinine levels in patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m²) receiving intravenous delafloxacin. If serum creatinine level increases occur, consider changing to oral delafloxacin. Discontinue BAXDELA if eGFR decreases to <15 mL/min/1.73 m² (8.6).