

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).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

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FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL

NERVOUS SYSTEM EFFECTS and EXACERBATION OF MYASTHENIA GRAVIS
1 INDICATIONS AND USAGE

- 1.1 Acute Bacterial Skin and Skin Structure Infections
- 1.2 Usage
- 2 DOSAGE AND ADMINISTRATION**
 - 2.1 Important Administration Instructions
 - 2.2 Recommended Dosage Regimen
 - 2.3 Dosage in Patients with Renal Impairment
 - 2.4 Preparation and Administration of BAXDELA for Injection Intravenous Solution
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Disabling and Potentially Irreversible Serious Adverse Reactions Including Tendinitis and Tendon Rupture, Peripheral Neuropathy and Central Nervous System Effects
 - 5.2 Tendinitis and Tendon Rupture
 - 5.3 Peripheral Neuropathy
 - 5.4 Central Nervous System Effects
 - 5.5 Exacerbation of Myasthenia Gravis
 - 5.6 Hypersensitivity Reactions
 - 5.7 *Clostridium difficile*-Associated Diarrhea
 - 5.8 Development of Drug-Resistant Bacteria
- 6 ADVERSE REACTIONS**
 - 6.1 Clinical Trials Experience
- 7 DRUG INTERACTIONS**
 - 7.1 Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment
- 8.7 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 BAXDELA for Injection
- 16.2 BAXDELA Tablets
- 16.3 Storage and Handling

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

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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)

1 INDICATIONS AND USAGE

1.1 Acute Bacterial Skin and Skin Structure Infections

BAXDELA is indicated in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following:

Gram-positive organisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Staphylococcus haemolyticus*, *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group (including *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), *Streptococcus pyogenes*, and *Enterococcus faecalis*.

Gram-negative organisms: *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

1.2 Usage

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 susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

BAXDELA Tablets

Administer BAXDELA at least 2 hours before or 6 hours after antacids containing magnesium, or aluminum, with sucralfate, with metal cations such as iron, or with multivitamin preparations containing zinc or iron, or with didanosine buffered tablets for oral suspension or the pediatric powder for oral solution [see *Drug Interactions (7.1)*].

BAXDELA Tablets can be taken with or without food [see *Clinical Pharmacology 12.3*].

If patients miss a dose, they should take it as soon as possible anytime up to 8 hours prior to their next scheduled dose. If less than 8 hours remain before the next dose, wait until their next scheduled dose.

BAXDELA for Injection

Do NOT administer BAXDELA for Injection with any solution containing multivalent cations, e.g., calcium and magnesium, through the same intravenous line [see *Drug Interactions (7.1)*]. Do NOT Co-infuse BAXDELA for Injection with other medications [see *Dosage and Administration (2.4)*].

2.2 Recommended Dosage Regimen

For treatment of adults with ABSSSI, the recommended dosage regimen of BAXDELA is as follows:

- Administer 300 mg of BAXDELA for Injection every 12 hours over 60 minutes by intravenous infusion for 5 to 14 days or,
- Administer 300 mg of BAXDELA for Injection every 12 hours over 60 minutes by intravenous infusion, then *switch* to a 450 mg BAXDELA tablet orally every 12 hours at the discretion of the physician for a total duration of 5 to 14 days or,
- Administer a 450 mg BAXDELA tablet orally every 12 hours for a total duration of 5 to 14 days.

2.3 Dosage in Patients with Renal Impairment

Table 1 below describes the dosage modification based on the estimated glomerular filtration rate (eGFR) that is recommended in patients with renal impairment. Dosage adjustment is required for patients with severe renal impairment (eGFR 15-29 mL/min/1.73m²).

In patients with severe renal impairment receiving BAXDELA intravenously, closely monitor serum creatinine levels and eGFR [see *Use in Specific Populations (8.7)*]. If serum creatinine level increases, consider switching to BAXDELA Tablets. Discontinue BAXDELA if eGFR decreases to <15 mL/min/1.73 m².

Table 1 Dosage Adjustment of BAXDELA in Patients with Renal Impairment

Estimated Glomerular Filtration Rate (eGFR) (mL/min/1.73 m ²) ^a	Recommended Dosage Regimen ^c	
	BAXDELA Tablets	BAXDELA for Injection ^b
30-89	No dosage adjustment	No dosage adjustment
15-29	No dosage adjustment	200 mg every 12 hours <u>Or</u> 200 mg every 12 hours, then switch to a 450 mg BAXDELA tablet orally every 12 hours at the discretion of the physician
End Stage Renal Disease (ESRD) (<15), including patients on hemodialysis (HD)	Not Recommended ^d	
<p>a. As calculated using the MDRD eGFR equation as follows: $eGFR (mL/min/1.73m^2) = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$</p> <p>b. All doses of BAXDELA are administered by intravenous infusion over 60 minutes.</p> <p>c. For a total treatment duration of 5 to 14 days.</p> <p>d. Not recommended due to insufficient information to provide dosing recommendations</p>		

2.4 Preparation and Administration of BAXDELA for Injection Intravenous Solution

Reconstitution and Dilution

1. BAXDELA must be reconstituted and then further diluted under aseptic conditions. Reconstitute the powder in the BAXDELA vial using 10.5 mL of 5% Dextrose Injection (D5W) or 0.9% Sodium Chloride Injection for each 300 mg vial. Shake the vial vigorously until contents are completely dissolved. The reconstituted vial contains 300 mg per 12 mL (25 mg/mL) of BAXDELA as a clear yellow to amber colored solution.
2. The reconstituted solution must then be diluted to a total volume of 250 mL using either 0.9% Sodium Chloride or D5W to achieve a concentration of 1.2 mg/mL, prior to administration. Prepare the required dose for intravenous infusion by withdrawing the appropriate volume from the reconstituted vial per [Table 2](#) below:

Table 2 Preparation of BAXDELA Doses

BAXDELA for Injection Dose	Volume of Reconstituted Solution to Withdraw
300 mg	12 mL
200 mg	8 mL

3. Aseptically transfer the required volume of BAXDELA reconstituted solution from the vial to an intravenous bag to achieve a 250 mL volume of infusion solution. Discard any unused portion of the reconstituted solution.
4. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Storage of the Reconstituted and Diluted Solutions

Reconstituted vials, as described above, may be stored either refrigerated at 2°C to 8°C (36°F to 46°F), or at controlled room temperature 20°C to 25°C (68°F to 77°F) for up to 24 hours. Do not freeze.

Once diluted into the intravenous bag, as described above, BAXDELA may be stored either refrigerated at 2°C to 8°C (36°F to 46°F) or at a controlled room temperature of 20°C to 25°C (68°F to 77°F) for up to 24 hours. Do not freeze.

Administration

After reconstitution and dilution, administer BAXDELA by intravenous infusion, using a total infusion time of 60 minutes [*see Dosage and Administration (2.1)*].

The compatibility of reconstituted BAXDELA with intravenous medications, additives, or substances other than D5W or 0.9% Sodium Chloride Injection has not been established. If a common intravenous line is being used to administer other drugs in addition to BAXDELA the line should be flushed before and after each BAXDELA infusion with 0.9% Sodium Chloride Injection or D5W.

3 DOSAGE FORMS AND STRENGTHS

BAXDELA for Injection: A sterile, lyophilized powder containing 300 mg delafloxacin (equivalent to 433 mg delafloxacin meglumine) in a single-dose vial which must be reconstituted and further diluted prior to intravenous infusion. The lyophilized powder is a light yellow to tan cake, which may exhibit cracking and shrinkage and slight variation in texture and color.

BAXDELA Tablets: Modified capsule shaped tablets in beige to mottled beige color with RX3341 debossed on one side containing 450 mg delafloxacin (equivalent to 649 mg delafloxacin meglumine).

4 CONTRAINDICATIONS

BAXDELA is contraindicated in patients with known hypersensitivity to delafloxacin or any of the fluoroquinolone class of antibacterial drugs, or any of the components of BAXDELA [*see Warnings and Precautions (5.6)*].

5 WARNINGS AND PRECAUTIONS

5.1 Disabling and Potentially Irreversible Serious Adverse Reactions Including Tendinitis and Tendon Rupture, Peripheral Neuropathy and Central Nervous System Effects

Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). These reactions could occur within hours to weeks after starting a fluoroquinolone. Patients of any age or without pre-existing risk factors have experienced these adverse reactions [*see Warnings and Precautions (5.2, 5.3 and 5.4)*].

Discontinue BAXDELA immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including BAXDELA, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.

5.2 Tendinitis and Tendon Rupture

Fluoroquinolones have been associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and has also been reported with the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendons. Tendinitis or tendon rupture can occur, within hours or days of starting a fluoroquinolone, or as long as several months after completion of fluoroquinolone therapy. Tendinitis and tendon rupture can occur bilaterally.

This risk of developing fluoroquinolone-associated tendinitis and tendon rupture is increased in patients over age 60 years of age, in patients taking corticosteroid drugs, and, in patients with kidney, heart, and lung

transplant. Other factors that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors.

Discontinue BAXDELA immediately if the patient experiences pain, swelling, inflammation or rupture of a tendon. Advise patients, at the first sign of tendon pain, swelling, or inflammation, to stop taking BAXDELA, to avoid exercise and use of the affected area, and to promptly contact their healthcare provider about changing to a non-quinolone antimicrobial drug. Avoid BAXDELA in patients who have a history of tendon disorders or have experienced tendinitis or tendon rupture.

5.3 Peripheral Neuropathy

Fluoroquinolones have been associated with an increased risk of peripheral neuropathy. Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias, and weakness have been reported in patients receiving fluoroquinolones, including BAXDELA. Symptoms may occur soon after initiation of fluoroquinolones and may be irreversible in some patients [*see Warnings and Precautions (5.1) and Adverse Reactions (6.1)*].

Discontinue BAXDELA immediately if the patient experiences symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation and/or motor strength in order to minimize the development of an irreversible condition. Avoid fluoroquinolones, including BAXDELA in patients who have previously experienced peripheral neuropathy [*see Adverse Reactions (6.1)*].

5.4 Central Nervous System Effects

Fluoroquinolones have been associated with an increased risk of central nervous system (CNS) reactions, including: convulsions and increased intracranial pressure (including pseudotumor cerebri) and toxic psychosis. Fluoroquinolones, including BAXDELA, may also cause CNS reactions of nervousness, agitation, insomnia, anxiety, nightmares, paranoia, dizziness, confusion, tremors, hallucinations, depression, and suicidal thoughts or acts. These adverse reactions may occur following the first dose. If these reactions occur in patients receiving BAXDELA, discontinue BAXDELA immediately and institute appropriate measures. As with all fluoroquinolones, use BAXDELA when the benefits of treatment exceed the risks in patients with known or suspected CNS disorders (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold.

5.5 Exacerbation of Myasthenia Gravis

Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Post-marketing serious adverse reactions, including death and requirement for ventilator support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid BAXDELA in patients with known history of myasthenia gravis [*see Patient Counseling Information (17)*].

5.6 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving fluoroquinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Hypersensitivity reactions have been reported in patients receiving BAXDELA. These reactions may occur after first or subsequent doses of BAXDELA [*see Adverse Reactions (6.1)*]. Discontinue BAXDELA at the first appearance of a skin rash or any other sign of hypersensitivity.

5.7 *Clostridium difficile*-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported in users of nearly all systemic antibacterial drugs, including BAXDELA, with severity ranging from mild diarrhea to fatal colitis. Treatment with antibacterial agents can alter the normal flora of the colon, and may permit overgrowth of *C. difficile*.

C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* should be discontinued, if possible. Appropriate measures such as fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated

5.8 Development of Drug-Resistant Bacteria

Prescribing BAXDELA in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6 ADVERSE REACTIONS

The following serious and otherwise important adverse reactions are discussed in greater detail in other sections of labeling:

- Disabling and Potentially Irreversible Serious Adverse Reactions [see *Warnings and Precautions (5.1)*]
- Tendinitis and Tendon Rupture [see *Warnings and Precautions (5.2)*]
- Peripheral Neuropathy [see *Warnings and Precautions (5.3)*]
- Central Nervous System Effects [see *Warnings and Precautions (5.4)*]
- Hypersensitivity Reactions [see *Warnings and Precautions (5.6)*]
- *Clostridium difficile*-Associated Diarrhea [see *Warnings and Precautions (5.7)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of BAXDELA cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice.

BAXDELA was evaluated in two multicenter, multinational, randomized, double-blind, double-dummy, non-inferiority trials (Trial 1 and Trial 2) in adults with ABSSSI. In Trial 1 patients received BAXDELA 300 mg by intravenous infusion every 12 hours and in Trial 2 the patients received BAXDELA 300 mg by intravenous infusion every 12 hours for 6 doses then were switched to BAXDELA 450 mg tablets every 12 hours. The total treatment duration was 5 to 14 days. Adverse reactions were evaluated for 741 patients treated with BAXDELA and 751 patients treated with comparator antibacterial drugs. The median age of patients treated with BAXDELA was 49 years, ranging between 18 and 94 years old; 15% were age 65 years and older. Patients treated with BAXDELA were predominantly male (62%) and Caucasian (86%). The BAXDELA treated population included 44% obese patients (BMI \geq 30 kg/m²), 11% with diabetes, and 16% with baseline renal impairment (calculated creatinine clearance less than 90 mL/min).

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation

Serious adverse reactions occurred in 3/741 (0.4%) of patients treated with BAXDELA and in 6/751 (0.8%) of patients treated with the comparator.

BAXDELA was discontinued due to an adverse reaction in 7/741 (0.9%) patients and the comparator was discontinued due to an adverse reaction in 21/751 (2.8%) patients. The most commonly reported adverse reactions leading to study discontinuation in the BAXDELA arm included urticaria (2/741; 0.3%) and hypersensitivity (2/741; 0.3%); whereas, the most commonly reported adverse reactions leading to study discontinuation in the comparator arm included urticaria (5/751; 0.7%), rash (4/751; 0.5%), hypersensitivity and infusion site extravasation (2/751; 0.3%).

Most Common Adverse Reactions

The most common adverse reactions in patients treated with BAXDELA were nausea (8%), diarrhea (8%), headache (3%), transaminase elevations (3%), and vomiting (2%). [Table 3](#) lists selected adverse reactions occurring in $\geq 2\%$ of patients receiving BAXDELA in the pooled adult Phase 3 clinical trials.

Table 3 Selected Adverse Reactions Occurring in $\geq 2\%$ of Patients Receiving BAXDELA in the Pooled Adult Phase 3 ABSSSI Clinical Trials

Adverse Reactions	BAXDELA N = 741 (%)	Vancomycin/aztreonam N = 751 (%)
Nausea	8%	6%
Diarrhea	8%	3%
Headache [#]	3%	6%
Transaminase Elevations*	3%	4%
Vomiting	2%	2%

[#]The data are not an adequate basis for comparison of rates between the study drug and the active control.

*Pooled reports include hypertransaminasaemia, increased transaminases, and increased ALT and AST.

Adverse Reactions Occurring in Less Than 2% of Patients Receiving BAXDELA in Phase 3 Clinical Trials

The following selected adverse reactions were reported in BAXDELA-treated patients at a rate of less than 2% in these clinical trials.

Cardiac Disorders: sinus tachycardia, palpitations, bradycardia

Ear and Labyrinth Disorders: tinnitus, vertigo

Eye Disorders: vision blurred

General disorders and administration site conditions: infusion site extravasation, infusion site bruise, discomfort, edema, erythema, irritation, pain, phlebitis, swelling, or thrombosis

Gastrointestinal Disorders: abdominal pain, dyspepsia

Immune System Disorders: hypersensitivity

Infections and Infestations: *Clostridium difficile* infection, fungal infection, oral candidiasis, vulvovaginal candidiasis

Laboratory Investigations: blood alkaline phosphatase increased, blood creatinine increased, blood creatine phosphokinase increased

Metabolism and Nutrition Disorders: hyperglycemia, hypoglycemia

Musculoskeletal and Connective Tissue Disorders: myalgia

Nervous System Disorders: dizziness, hypoesthesia, paraesthesia, dysgeusia, presyncope, syncope

Psychiatric Disorders: anxiety, insomnia, abnormal dreams

Renal and Urinary: renal impairment, renal failure

Skin and Subcutaneous Tissue Disorders: pruritus, urticaria, dermatitis, rash

Vascular Disorders: flushing, hypotension, hypertension, phlebitis

7 DRUG INTERACTIONS

7.1 Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins

Fluoroquinolones form chelates with alkaline earth and transition metal cations. Oral administration of BAXDELA with antacids containing aluminum or magnesium, with sucralfate, with metal cations such as iron, or with multivitamins containing iron or zinc, or with formulations containing divalent and trivalent cations such as didanosine buffered tablets for oral suspension or the pediatric powder for oral solution, may substantially interfere with the absorption of BAXDELA, resulting in systemic concentrations considerably lower than desired. Therefore, BAXDELA should be taken at least 2 hours before or 6 hours after these agents [*see Dosage and Administration (2.1)*].

There are no data concerning an interaction of intravenous BAXDELA with oral antacids, sucralfate, multivitamins, didanosine, or metal cations. However, BAXDELA should not be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same intravenous line [*see Dosage and Administration (2.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data with BAXDELA use in pregnant women are insufficient to inform a drug-associated risk of major birth defects and miscarriages. When delafloxacin (as the N-methyl glucamine salt) was administered orally to rats during the period of organogenesis, no malformations or fetal death were observed at up to 7 times the estimated clinical exposure based on AUC. When rats were dosed intravenously in late pregnancy and through lactation, there were no adverse effects on offspring at exposures approximating the clinical intravenous (IV) exposure based on AUC [*see Data*].

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Data

Animal Data

In embryo-fetal studies, oral administration of delafloxacin to pregnant rats during the period of major organogenesis resulted in maternal toxicity and reduced fetal body weights at the highest dose (1600 mg/kg/day) and fetal ossification delays at all doses. No malformations were reported up to the highest dose tested (approximately 7 times the estimated human plasma exposure based on AUC). The lowest dose, 200 mg/kg/day (approximately 2.5 times the estimated human plasma exposure based on AUC), was still toxic to the fetus, based on ossification delays. In rabbits, a species known to be extremely sensitive to maternal toxicity of antibacterial drugs, no embryo-fetal developmental toxicity was observed up to the highest dose which induced maternal toxicity (1.6 mg/kg/day, or approximately 0.01 times the estimated human plasma exposure based on AUC). In a pre-postnatal study in rats of IV administered delafloxacin, dams at the highest dose tested (120 mg/kg/day) exhibited slightly lower body weights and slightly longer gestation length than control animals. Exposure at that dose was estimated to be approximately 5 times human plasma exposure based on AUC, as determined in a separate shorter term study at an earlier stage of pregnancy. Effects on pups at that dose included increased mortality during lactation, small stature, and lower body weights, but no changes in learning and memory, sensory function, locomotor activity, developmental landmarks, or reproductive performance were reported. The No Adverse Effect Level (NOAEL) for maternal toxicity pup development in that study was 60 mg/kg/day (approximately 580 mg/day IV for a 60 kg patient, or just below the clinical IV dose).

8.2 Lactation

Risk Summary

There are no data available on the presence of delafloxacin in human milk, the effects on the breast-fed infant, or the effects on milk production. Delafloxacin is excreted in the breast milk of rats [*see Data*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BAXDELA and any potential adverse effects on the breast-fed child from BAXDELA or from the underlying maternal condition.

Data

After single oral dose of 20 mg/kg (approximately 194 mg for a 60 kg patient) ¹⁴C labeled delafloxacin on post-natal day 11, the radioactivity was transferred into the milk of lactating rats. The mean milk/plasma radioactivity concentration ratios in dams at 4 and 8 hours after dosing were 8.5 and 4.0, respectively, and essentially background by 24 hours. The rate of elimination of radioactivity was similar in milk and plasma. Absorption of radioactive drug by rat pups following nursing was observed.

8.4 Pediatric Use

Use in patients under 18 years of age is not recommended. Safety and effectiveness in pediatric patients below the age of 18 years have not been established. Pediatric studies were not conducted because risk-benefit considerations do not support the use of BAXDELA for ABSSSI in this population. Fluoroquinolones cause arthropathy in juvenile animals.

8.5 Geriatric Use

Of the 754 adults patients treated with BAXDELA in the Phase 3 ABSSSI trials, 111 (15%) were ≥ 65 years of age. The clinical response rates at 48-72 hours in the BAXDELA group (ITT Population) in patients aged ≥ 65 years old were 75.7% and 82.3% in patients aged < 65 years old; comparator response rates were 71.3% in patients aged ≥ 65 years old and 82.1% in patients aged < 65 years old.

In the safety population, of the 741 adult patients treated with BAXDELA, 110 (16.4%) patients aged ≥ 65 years old and 146 (23.1%) patients aged < 65 years old had at least one adverse drug reaction.

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolones. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing BAXDELA to elderly patients especially those on corticosteroids. Patients should be informed of this potential adverse reaction and advised to discontinue BAXDELA and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur [*see Warnings and Precautions (5.1)*].

In elderly subjects (≥ 65 years), the mean C_{max} and AUC_{∞} of delafloxacin were about 35% higher compared with young adults, which is not considered clinically significant [*see Clinical Pharmacology (12.3)*].

8.6 Hepatic Impairment

No dosage adjustment is necessary for BAXDELA in patients with hepatic impairment [*see Clinical Pharmacology (12.3)*]

8.7 Renal Impairment

No dosage adjustment of BAXDELA is necessary in patients with mild (eGFR 60-89 mL/min/1.73 m²) or moderate (eGFR 30-59 mL/min/1.73 m²) renal impairment. The dose of BAXDELA intravenous IV infusion in

patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m²) should be decreased to 200 mg intravenously every 12 hours; the dose of oral BAXDELA in patients with severe renal impairment (eGFR 15-29 mL/min/1.73 m²) is 450mg orally every 12 hours. BAXDELA is not recommended in patients with End Stage Renal Disease [ESRD] (eGFR of <15 mL/min/1.73 m²) [see *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)*].

In patients with severe renal impairment or ESRD (eGFR of < 15 mL/min/1.73 m²), accumulation of the intravenous vehicle, sulfobutylether-β-cyclodextrin (SBECD) occurs. Serum creatinine levels should be closely monitored in patients with severe renal impairment receiving intravenous BAXDELA. If serum creatinine level increases occur, consideration should be given to changing to oral BAXDELA. If eGFR decreases to <15 mL/min/1.73 m², BAXDELA should be discontinued.

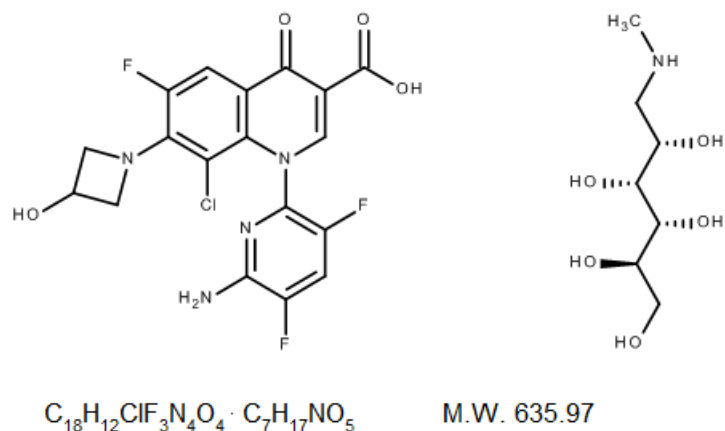
10 OVERDOSAGE

Treatment of overdose with BAXDELA should consist of observation and general supportive measures. Hemodialysis removed about 19% of delafloxacin and 56% of SBECD (Sulfobutylether β cyclodextrin) after intravenous administration of BAXDELA. [see *Clinical Pharmacology (12.3)*]

11 DESCRIPTION

BAXDELA (delafloxacin) for Injection and BAXDELA (delafloxacin) Tablets contain meglumine salt of delafloxacin, a fluoroquinolone antibacterial. Delafloxacin meglumine is identified chemically as 1-Deoxy-1-(methylamino)-D-glucitol, 1-(6-amino-3,5-difluoropyridin-2-yl)-8-chloro-6-fluoro-7-(3-hydroxyazetid-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (salt), the chemical structure of which is shown below. The meglumine salt has a molecular weight of 635.97 g/mol, whereas the molecular weight of the delafloxacin free acid is 440.76 g/mol.

Figure 1 Chemical Structure



BAXDELA is intended for intravenous infusion or oral administration. BAXDELA is supplied as a sterile, lyophilized powder for injection and oral tablets as follows:

BAXDELA for Injection

Each vial of BAXDELA for Injection, 300 mg, is a sterile lyophilized powder that contains 300 mg delafloxacin (equivalent to 433 mg delafloxacin meglumine) and the following inactive ingredients: Edetate disodium (EDTA), (3.4 mg); meglumine (59 mg); sulfobutylether-β-cyclodextrin (2400 mg).

BAXDELA Tablets

Each BAXDELA tablet for oral use contains 450 mg delafloxacin (equivalent to 649 mg delafloxacin meglumine) and the following inactive ingredients: Citric acid anhydrous (5.5 mg); crospovidone (109 mg); magnesium stearate (10 mg); microcrystalline cellulose (417 mg); povidone (34 mg); sodium bicarbonate (140 mg); sodium phosphate monobasic monohydrate (5.5 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BAXDELA is an antibacterial drug [see *Microbiology* (12.4)].

12.2 Pharmacodynamics

The antibacterial activity of delafloxacin appears to best correlate with the ratio of area under the concentration-time curve of free delafloxacin to minimal inhibitory concentration ($fAUC/MIC$) for Gram-positive organisms such as *Staphylococcus aureus* and Gram-negative organisms such as *Escherichia coli* based on animal models of infection.

Cardiac Electrophysiology

In a randomized, positive- and placebo-controlled, thorough QT/QTc study, 51 healthy subjects received BAXDELA 300 mg IV, BAXDELA 900 mg IV, oral moxifloxacin 400 mg, or placebo. Neither BAXDELA 300 mg nor BAXDELA 900 mg (three times the intravenous therapeutic dose) had any clinically relevant adverse effect on cardiac repolarization.

Photosensitivity Potential

A study of photosensitizing potential to ultraviolet (UVA and UVB) and visible radiation was conducted in 52 healthy volunteers (originally 13 subjects per treatment group). BAXDELA, at 200 mg/day and 400 mg/day (0.22 and 0.44 times the approved recommended daily oral dosage, respectively) for 7 days, and placebo did not demonstrate clinically significant phototoxic potential at any wavelengths tested (295 nm to 430 nm), including solar simulation. The active comparator (lomefloxacin) demonstrated a moderate degree of phototoxicity at UVA 335 nm and 365 nm and solar simulation wavelengths.

12.3 Pharmacokinetics

The pharmacokinetic parameters of delafloxacin following single- and multiple-dose (every 12 hours) oral (450 mg) and intravenous (300 mg) administration are shown in Table 4. Steady-state was achieved within approximately three days with accumulation of approximately 10% and 36% following IV and oral administration, respectively.

Table 4 Mean (SD) Delafloxacin Pharmacokinetic Parameters Following Single and Multiple Oral and Intravenous Administration

Parameters	Tablet		Intravenous Injection	
	Single Dose 450 mg	Steady State 450 mg Q12h [§]	Single Dose 300 mg	Steady State 300 mg Q12h [§]
T _{max} (h) [†]	0.75 (0.5, 4.0)	1.00 (0.50, 6.00)	1.0 (1.0, 1.2)	1.0 (1.0, 1.0)
C _{max} (µg/mL)	7.17 (2.01)	7.45 (3.16)	8.94 (2.54)	9.29 (1.83)
AUC (µg•h/mL) [‡]	22.7 (6.21)	30.8 (11.4)	21.8 (4.54)	23.4 (6.90)
CL or CL/F(L/h) ^{&}	20.6 (6.07)	16.8 (6.54)	14.1 (2.81)	13.8 (3.96)
CL _r (L/h)	-		5.89 (1.53)	6.69 (2.19)
R _{ac}		1.36		1.1

C_{max} = maximum concentration; T_{max} = time to reach C_{max} ; AUC = area under the concentration-time curve; CL = systemic clearance; CL/F = apparent oral clearance; R_{ac} = accumulation ratio

† Median (range)

‡ AUC is AUC_{τ} (AUC from time 0 to 12 hours) for single dose and multiple-dose administration

& CL is reported for intravenous injection. CL/F is reported for tablet

§ Q12h is every 12 hours

Absorption

The absolute bioavailability for BAXDELA 450 mg oral tablet administered as a single dose was 58.8%. The AUC of delafloxacin following administration of a single 450 mg oral (tablet) dose was comparable to that following a single 300 mg intravenous dose. The C_{max} of delafloxacin was achieved within about 1 hour after oral administration under fasting condition. Food (kcal:917, Fat: 58.5%, Protein: 15.4%, Carbohydrate: 26.2%) did not affect the bioavailability of delafloxacin [see *Dosage and Administration (2.1)*].

Distribution

The steady state volume of distribution of delafloxacin is 30–48 L which approximates total body water. The plasma protein binding of delafloxacin is approximately 84%; delafloxacin primarily binds to albumin. Plasma protein binding of delafloxacin is not significantly affected by renal impairment.

Elimination

In a mass balance study, the mean half-life for delafloxacin was 3.7 hours (SD 0.7 hour) after a single dose intravenous administration. The mean half-life values for delafloxacin ranged from 4.2 to 8.5 hours following multiple oral administrations. Following administration of a single 300 mg intravenous dose of BAXDELA, the mean clearance (CL) of delafloxacin was 16.3 L/h (SD 3.7 L/h), and the renal clearance (CL_r) of delafloxacin accounts for 35-45% of the total clearance.

Metabolism

Glucuronidation of delafloxacin is the primary metabolic pathway with oxidative metabolism representing about 1% of an administered dose. The glucuronidation of delafloxacin is mediated mainly by UGT1A1, UGT1A3, and UGT2B15. Unchanged parent drug is the predominant component in plasma. There are no significant circulating metabolites in humans.

Excretion

After single intravenous dose of ¹⁴C-labeled delafloxacin, 65% of the radioactivity was excreted in urine as unchanged delafloxacin and glucuronide metabolites and 28% was excreted in feces as unchanged delafloxacin. Following a single oral dose of ¹⁴C-labeled delafloxacin, 50% of the radioactivity was excreted in urine as unchanged delafloxacin and glucuronide metabolites and 48% was excreted in feces as unchanged delafloxacin.

Specific Populations

Based on a population pharmacokinetic analysis, the pharmacokinetics of delafloxacin were not significantly impacted by age, sex, race, weight, body mass index, and disease state (ABSSSI).

Patients with Hepatic Impairment

No clinically meaningful changes in delafloxacin C_{max} and AUC were observed, following administration of a single 300-mg intravenous dose of BAXDELA to patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B, and C) compared to matched healthy control subjects.

Patients with Renal Impairment

Following a single intravenous (300 mg) administration of delafloxacin to subjects with mild (eGFR = 51-80 mL/min/1.73 m²), moderate (eGFR = 31–50 mL/min/1.73 m²), severe (eGFR = 15-29 mL/min/1.73 m²) renal impairment, and ESRD on hemodialysis receiving intravenous delafloxacin within 1 hour before and 1 hour after hemodialysis, mean total exposure (AUC_t) of delafloxacin was 1.3, 1.6, 1.8, 2.1, and 2.6-fold higher, respectively than that for matched normal control subjects. The mean dialysate clearance (CL_d) of delafloxacin was 4.21 L/h (SD 1.56 L/h). After about 4 hours of hemodialysis, the mean fraction of administered delafloxacin recovered in the dialysate was about 19% [see *Use in Specific Populations* (8.7)].

Following a single oral (400 mg) administration of delafloxacin to subjects with mild (eGFR = 51-80 mL/min/1.73 m²), moderate (eGFR = 31-50 mL/min/1.73 m²), or severe (eGFR = 15-29 mL/min/1.73 m²) renal impairment, the mean total exposure (AUC_t) of delafloxacin was about 1.5-fold higher for subjects with moderate and severe renal impairment compared with healthy subjects, whereas total systemic exposures of delafloxacin in subjects with mild renal impairment were comparable with healthy subjects.

In patients with moderate (eGFR = 31–50 mL/min/1.73 m²), or severe (eGFR = 15–29 mL/min/1.73 m²) renal impairment or ESRD on hemodialysis, accumulation of the intravenous vehicle SBECD occurs. The mean systemic exposure (AUC) increased 2-fold, 5-fold, 7.5-fold, and 27-fold for patients with moderate impairment, severe impairment, ESRD on hemodialysis receiving intravenous delafloxacin within 1 hour before, and 1 hour after hemodialysis respectively, compared to the healthy control group. In subjects with ESRD undergoing hemodialysis, SBECD is dialyzed with a clearance of 4.74 L/h. When hemodialysis occurred 1 hour after the BAXDELA infusion in subjects with ESRD, the mean fraction of SBECD recovered in the dialysate was 56.1% over approximately 4 hours.

Geriatric Patients

Following single oral administration of 250 mg delafloxacin (approximately 0.6 times the approved recommended oral dose), the mean delafloxacin C_{max} and AUC_∞ values in elderly subjects (≥ 65 years) were about 35% higher compared to values obtained in young adults (18 to 40 years). This difference is not considered clinically relevant. A population pharmacokinetic analysis of patients with ABSSSI showed no significant impact of age on delafloxacin pharmacokinetics.

Male and Female Patients

Following single oral administration of 250 mg delafloxacin (approximately 0.6 times the approved recommended oral dose), the mean delafloxacin C_{max} and AUC_∞ values in male subjects were comparable to female subjects. Results from a population pharmacokinetic analysis showed that females have a 24% lower AUC than males. This difference is not considered clinically relevant.

Drug Interaction Studies

Drug Metabolizing Enzymes

Delafloxacin at clinically relevant concentrations does not inhibit the cytochrome P450 isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 in vitro in human liver microsomes. At a delafloxacin concentration (500 μM) well above clinically relevant exposures, the activity of CYP2E1 was increased.

In human hepatocytes, delafloxacin showed no potential for in vitro induction of CYP1A2, 2B6, 2C19, or 2C8 but was a mild inducer of CYP2C9 at a concentration of 100 μM and CYP3A4 at a clinically relevant concentration. Administration of BAXDELA 450 mg every 12 hours for 5 days to healthy male and female subjects (n = 22) prior to and on Day 6 with a single oral 5-mg dose of midazolam (a sensitive CYP3A

substrate), did not affect the C_{max} and AUC values for midazolam or 1-hydroxy midazolam compared to administration of midazolam alone.

Transporters

Delafloxacin was not an inhibitor of the following hepatic and renal transporters in vitro at clinically relevant concentrations: MDR1, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, BSEP, OCT1 and OCT2. Delafloxacin was not a substrate of OAT1, OAT3, OCT1, OCT2, OATP1B1 or OATP. Delafloxacin was shown to be a substrate of P-gp and BCRP in vitro. The clinical relevance of co-administration of delafloxacin and P-gp and/or BCRP inhibitors is unknown.

12.4 Microbiology

Mechanism of Action

Delafloxacin belongs to the fluoroquinolone class of antibacterial drugs and is anionic in nature. The antibacterial activity of delafloxacin 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. Delafloxacin exhibits a concentration-dependent bactericidal activity against gram-positive and gram-negative bacteria in vitro.

Resistance

Resistance to fluoroquinolones, including delafloxacin, can occur due to mutations in defined regions of the target bacterial enzymes topoisomerase IV and DNA gyrase referred to as Quinolone-Resistance Determining Regions (QRDRs), or through altered efflux.

Fluoroquinolones, including delafloxacin, have a different chemical structure and mechanism of action relative to other classes of antibacterial compounds (e.g. aminoglycosides, macrolides, β-lactams, glycopeptides, tetracyclines and oxazolidinones).

In vitro resistance to delafloxacin develops by multiple step mutations in the QRDRs of gram-positive and gram-negative bacteria. Delafloxacin-resistant mutants were selected in vitro at a frequency of 10^{-9}.

Although cross-resistance between delafloxacin and other fluoroquinolone-class antibacterial agents has been observed, some isolates resistant to other fluoroquinolone-class antibacterial agents may be susceptible to BAXDELA.

Interaction With Other Antimicrobials

In vitro drug combination studies with delafloxacin and aztreonam, ceftazidime, colistin, daptomycin, linezolid, meropenem, tigecycline, trimethoprim/sulfamethoxazole and vancomycin demonstrated neither synergy nor antagonism.

Antimicrobial Activity

BAXDELA has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections, [see *Indications and Usage (1)*].

Aerobic bacteria

Gram-positive bacteria

Staphylococcus aureus (including methicillin-resistant and methicillin-sensitive strains)

Staphylococcus haemolyticus

Staphylococcus lugdunensis

Streptococcus pyogenes

Streptococcus agalactiae

Streptococcus anginosus Group (including *S. anginosus*, *S. intermedius*, and *S. constellatus*)

Enterococcus faecalis

Gram-negative bacteria

Escherichia coli

Klebsiella pneumoniae

Enterobacter cloacae

Pseudomonas aeruginosa

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint of delafloxacin against isolates of similar genus or organism group. However, the efficacy of BAXDELA in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Aerobic bacteria

Gram-positive bacteria

Streptococcus dysgalactiae

Gram-negative bacteria

Enterobacter aerogenes

Haemophilus parainfluenzae

Klebsiella oxytoca

Proteus mirabilis

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative reports of in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid in the selection of an appropriate antibacterial drug for treatment.

Dilution Techniques

Quantitative methods are used to determine MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method ^{1,3} (broth and/or agar). The MIC values should be interpreted according to criteria provided in [Table 5](#).

Diffusion Techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method ^{2,3}. This procedure uses paper disks impregnated with 5 mcg of delafloxacin to test the susceptibility of bacteria to delafloxacin. The disk diffusion breakpoints are provided in [Table 5](#).

Table 5 Susceptibility Test Interpretive Criteria for delafloxacin

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (Zone Diameter in mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (methicillin-resistant and methicillin-susceptible isolates)	≤ 0.25	0.5	≥ 1	≥ 23	20-22	≤ 19
<i>Staphylococcus haemolyticus</i>	≤ 0.25	0.5	≥ 1	≥ 24	21-23	≤ 20
<i>Streptococcus pyogenes</i> ^a	≤ 0.06	-	-	≥ 20	-	-
<i>Streptococcus agalactiae</i>	≤ 0.06	0.12	≥ 0.25		-	
<i>Streptococcus anginosus</i> Group ^{a, b}	≤ 0.06	-	-	≥ 25	-	-
<i>Enterococcus faecalis</i>	≤ 0.12	0.25	≥ 0.5	≥ 21	19-20	≤ 18
<i>Enterobacteriaceae</i> ^c	≤ 0.25	0.5	≥ 1	≥ 22	19-21	≤ 18
<i>Pseudomonas aeruginosa</i>	≤ 0.5	1	≥ 2	≥ 23	20-22	≤ 19

S = susceptible; I = intermediate; R = resistant

^aThe current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC results other than "Susceptible" should be submitted to a reference laboratory for further testing.

^b includes: *S. anginosus*, *S. constellatus* and *S. intermedius*

^c *E. coli*, *K. pneumoniae*, and *E. cloacae* only.

A report of *Susceptible* (S) indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of *Intermediate* (I) indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of the drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* (R) indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test^{1,2,3}. Standard delafloxacin powder should provide the following range of MIC values noted in Table 5. For the diffusion technique using the 5 mcg delafloxacin disk, the criteria in Table 6 should be achieved.

Table 6 Acceptable Quality Control Ranges for Delafloxacin

	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
<i>Staphylococcus aureus</i> ATCC 29213	0.001–0.008	Not applicable
<i>Staphylococcus aureus</i> ATCC 25923	Not applicable	32–40
<i>Enterococcus faecalis</i> ATCC 29212	0.015–0.12	Not applicable
<i>Streptococcus pneumoniae</i> ATCC 49619	0.004–0.015	29–36
<i>Escherichia coli</i> ATCC 25922	0.008–0.03	28–35
<i>Pseudomonas aeruginosa</i> ATCC 27853	0.12–0.5	23–29
<i>Haemophilus influenzae</i> ATCC 49427	0.00025–0.001	40–51

ATCC = American Type Culture Collection

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies have not been conducted with BAXDELA.

Delafloxacin was not mutagenic in a bacterial reverse mutation (Ames) assay, and was not clastogenic in a mouse bone marrow micronucleus test at ≥ 15 times the estimated human plasma exposure based on AUC. In an in vitro clastogenicity assay using isolated human lymphocytes, delafloxacin was negative in short incubations (~3 hours) and, at high cytotoxic concentrations (> 1.0 mM), was positive in a long incubation (~19 hours).

Delafloxacin did not affect the fertility of male and female rats up to the highest intravenous dose tested (120 mg/kg/day); female rats were dosed 2 weeks prior to mating and through gestation day 7 and male rats were treated for 28 days prior to mating and beyond for a total of 58-59 days. AUC in male and female (non-pregnant and pregnant) rats at 120 mg/kg/day delafloxacin intravenous was estimated to be approximately 5 times the estimated human plasma exposure based on AUC in separate intravenous toxicology studies in rats, one of which was a 2-week study that used a different vehicle for delafloxacin than in the fertility study, and another was an 8-day study in nonpregnant and pregnant (gestation day 13) rats that used the same vehicle for delafloxacin as in the fertility study.

13.2 Animal Toxicology and/or Pharmacology

Fluoroquinolone antibacterials are associated with degenerative changes in articular cartilage and arthropathy in skeletally immature animals. In a toxicology study of the formulated tablet in dogs, the femoral head of one of three high dose (480 mg/kg/day) females had minimal focal degeneration of the superficial articular cartilage and a small focal cleft in the articular cartilage. No other joints were examined.

14 CLINICAL STUDIES

Acute Bacterial Skin and Skin Structure Infections

A total of 1510 adults with acute bacterial skin and skin structure infections (ABSSSI) were randomized in 2 multicenter, multinational, double-blind, double-dummy, non-inferiority trials. Trial 1 compared BAXDELA 300 mg via intravenous infusion every 12 hours to comparator. In Trial 2, patients received BAXDELA 300 mg via intravenous infusion every 12 hours for 6 doses then made a mandatory switch to oral BAXDELA 450 mg every 12 hours. In both studies, the comparator was the intravenous combination of vancomycin 15 mg/kg actual body weight and aztreonam. Aztreonam therapy was discontinued if no gram-negative pathogens were identified in the baseline cultures.

In Trial 1, 331 patients with ABSSSI were randomized to BAXDELA and 329 patients were randomized to vancomycin plus aztreonam. Patients in this trial had the following infections: cellulitis (39%), wound infection (35%), major cutaneous abscess (25%), and burn infection (1%). The overall mean surface area of the infected lesion as measured by digital planimetry was 307 cm². The average age of patients was 46 years (range 18 to 94 years). Patients were predominately male (63%) and White (91%); 32% had BMI ≥ 30 kg/m². The population studied in Trial 1 included a distribution of patients with associated comorbidities such as hypertension (21%), diabetes (9%), and renal impairment (16%; 0.2% with severe renal impairment or ESRD). Current or recent history of drug abuse, including IV drug abuse, was reported by 55% of patients. Bacteremia was documented at baseline in 2% of patients.

In Trial 2, 423 patients were randomized to BAXDELA and 427 patients were randomized to vancomycin plus aztreonam. Patients in this trial had the following infections: cellulitis (48%), wound infection (26%), major cutaneous abscess (25%), and burn infection (1%). The overall mean surface area of the infected lesion, as measured by digital planimetry, was 353 cm². The average age of patients was 51 years (range 18 to 93 years). Patients were predominately male (63%) and White (83%); 50 % had a BMI ≥ 30 kg/m². The population studied in Trial 2 included a distribution of patients with associated comorbidities such as hypertension (31%), diabetes (13%) and renal impairment (16%; 0.2% with severe renal impairment or ESRD). Current or recent history of drug abuse, including IV drug abuse, was reported by 30% of patients. Bacteremia was documented at baseline in 2% of patients.

In both trials, objective clinical response at 48 to 72 hours post initiation of treatment was defined as a 20% or greater decrease in lesion size as determined by digital planimetry of the leading edge of erythema. [Table 7](#) summarizes the objective clinical response rates in both of these trials.

Table 7 Clinical Response at 48–72 hours* in the ITT Population with ABSSSI in Trial 1 and Trial 2

Trial	BAXDELA (300 mg IV)	Vancomycin 15 mg/kg + Aztreonam	Treatment Difference† (2-sided 95% CI)
Trial 1			
Total n	331	329	
Responder, n (%)	259 (78.2%)	266 (80.9%)	-2.6 (-8.8, 3.6)
	BAXDELA (300 mg IV and 450 mg oral)	Vancomycin 15 mg/kg + Aztreonam	
Trial 2			
Total N	423	427	
Responder, n/N (%)	354 (83.7%)	344 (80.6%)	3.1 (-2.0, 8.3)

CI = Confidence Interval; ITT = Intent to Treat and includes all randomized patients

*Objective clinical response was defined as a 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 without any reasons for failure (less than 20% reduction in lesion size, administration of rescue antibacterial therapy, use of another antibacterial or surgical procedure to treat for lack of efficacy, or death). Missing patients were treated as failures.

†Treatment difference, expressed as percentage, and CI based on Miettinen and Nuriminen method without stratification.

In both trials, an investigator assessment of response was made at Follow-up (Day 14 ± 1) in the ITT and CE populations. Success was defined as “cure + improved,” where patients had complete or near resolution of signs and symptoms, with no further antibacterial needed. The success rates in the ITT and CE populations are shown in [Table 8](#).

Table 8 Investigator- Assessed Success at the Follow-up Visit in ABSSSI —ITT Population and CE Population in Trial 1 and 2

Trial	BAXDELA (300 mg IV)	Vancomycin 15 mg/kg + Aztreonam	Treatment Difference† (2-sided 95% CI)
Trial 1			
Success*, n/N (%) ITT	270/331 (81.6%)	274/329 (83.3%)	-1.7 (-7.6, 4.1)
Success*, n/N (%) CE	232/240 (96.7%)	238/244 (97.5%)	-0.9 (-4.3, 2.4)
	BAXDELA (300 mg IV and 450 mg Oral)	Vancomycin 15 mg/kg + Aztreonam	
Trial 2			
Success, n/N (%) ITT	369/423 (87.2%)	362/427 (84.8%)	2.5 (-2.2, 7.2)
Success, n/N (%) CE	339/353 (96.0%)	319/329 (97.0%)	-0.9 (-3.9, 2.0)

CI = confidence interval; ITT = intent to treat and includes all randomized patients; CE = clinically evaluable consisted of all ITT patients who had a diagnosis of ABSSSI, received at least 80% of expected doses of study drug, did not have any protocol deviations that would affect the assessment of efficacy and had investigator assessment at the Follow-Up Visit.

*Success was cure + improved where patients had complete or near resolution of signs and symptoms with no further antibacterial needed.

†Treatment difference, expressed as percentage, and CI based on Miettinen and Nurminen method without stratification.

Six delafloxacin patients had baseline *S. aureus* bacteremia with ABSSSI. Five of these 6 patients (83.3%) were clinical responders at 48 to 72 hours and 5/6 (83.3%) were considered clinical success for ABSSSI at Day 14 ± 1. Two delafloxacin patients had baseline Gram-negative bacteremia (*K. pneumoniae* and *P. aeruginosa*), and both were clinical responders and successes.

The investigator assessments of clinical success rates were also similar between treatment groups at Late Follow-up (LFU, day 21-28).

Objective clinical response and investigator-assessed success by baseline pathogens from the primary infection site or blood cultures for the microbiological ITT (MITT) patient population pooled across Trial 1 and Trial 2 are presented in [Table 9](#).

Table 9 Outcomes by Baseline Pathogen (Pooled across Trial 1 and Trial 2; MITT* Population)

Pathogen	Clinical Response ^a at 48–72 hours		Investigator-Assessed Success ^b at Follow-up	
	BAXDELA n/N (%)	Comparator n/N (%)	BAXDELA 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 ^c	149/177 (84.2)	148/183 (80.9)	154/177 (87.0)	153/183 (83.6)
Methicillin-resistant ^c	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>Staphylococcus haemolyticus</i>	11/15 (73.3)	7/8 (87.5)	13/15 (86.7)	7/8 (87.5)
<i>Streptococcus agalactiae</i>	10/14 (71.4)	9/12 (75.0)	12/14 (85.7)	11/12 (91.7)
<i>Streptococcus anginosus</i> Group	59/64 (92.2)	55/61 (90.2)	54/64 (84.4)	47/61 (77.0)
<i>Staphylococcus lugdunensis</i>	8/11 (72.7)	6/9 (66.7)	10/11 (90.9)	8/9 (88.9)
<i>Enterococcus faecalis</i>	11/11 (100.0)	12/16 (75.0)	9/11 (81.8)	14/16 (87.5)
<i>Escherichia coli</i>	12/14 (85.7)	16/20 (80.0)	12/14 (85.7)	18/20 (90.0)
<i>Enterobacter cloacae</i>	10/14 (71.4)	8/11 (72.7)	12/14 (85.7)	10/11 (90.9)
<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 a 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 (Day14±1).

*Microbiological ITT (MITT) consists of all randomized patients who had a baseline pathogen identified that is known to cause ABSSSI.

^c Discrepancy in the total numbers is due to the multiple subjects having both MRSA and MSSA isolates.

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Tenth Edition*. CLSI document M07-A10. Wayne, PA: Clinical and Laboratory Standards Institute; 2015
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Susceptibility Tests, Approved Standard – Twelfth Edition*. CLSI document M02-A12. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.
3. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing – 27th ed*. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2017.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 BAXDELA for Injection

BAXDELA is supplied as a sterile, lyophilized powder in single-dose clear glass vials of 300 mg delafloxacin (equivalent to 433 mg delafloxacin meglumine). The lyophilized powder is a light yellow to tan cake, which may exhibit cracking and shrinkage and slight variation in texture and color.

They are supplied as follows: 300-mg single-dose vials (NDC 70842-102-03), packaged in cartons of 10.

16.2 BAXDELA Tablets

BAXDELA Tablets contain 450 mg delafloxacin (equivalent to 649 mg delafloxacin meglumine); each modified capsule-shaped tablet in beige to mottled beige color is debossed with RX3341 on one side. They are supplied as follows:

Bottles of 20 tablets with child-resistant closure (NDC 70842-101-01)

Unit dose blister packs which contain 20 tablets (2 blister cards of 10 tablets each) (NDC 70842-101-02)

16.3 Storage and Handling

BAXDELA Tablets and BAXDELA for Injection should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*].

The reconstituted powder may be stored for up to 24 hours under refrigerated or controlled room temperature and then further diluted for intravenous infusion. The reconstituted solution in the infusion bag may be stored under refrigerated or controlled room temperature conditions for up to 24 hours [*see Dosage and Administration (2.4)*]. **Do not freeze.**

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide)

Serious Adverse Reactions

Advise patients to stop taking BAXDELA if they experience an adverse reaction and to call their healthcare provider for advice on completing the full course of treatment with another antibacterial drug.

Inform patients of the following serious adverse reactions that have been associated with BAXDELA or other fluoroquinolone use:

- Disabling and Potentially Irreversible Serious Adverse Reactions that may occur together: Inform patients that disabling and potentially irreversible serious adverse reactions, including tendinitis and tendon rupture, peripheral neuropathies, and central nervous system effects, have been associated with use of fluoroquinolones and may occur together in the same patient. Inform patients to stop taking BAXDELA immediately if they experience an adverse reaction and to call their healthcare provider.
- Tendinitis and Tendon Rupture: Instruct patients to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue BAXDELA treatment. Symptoms may be irreversible. The risk of severe tendon disorder with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.
- Peripheral Neuropathy: Inform patients that peripheral neuropathies have been associated with BAXDELA use, symptoms may occur soon after initiation of therapy and may be irreversible. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, immediately discontinue BAXDELA and tell them to contact their physician.
- Central Nervous System Effects: (for example, convulsions, dizziness, lightheadedness, increased intracranial pressure): Inform patients that convulsions have been reported in patients receiving fluoroquinolones, Instruct patients to notify their physician before taking this drug if they have a history of convulsions. Inform patients that they should know how they react to BAXDELA before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination. Instruct

patients to notify their physician if persistent headache with or without blurred vision occurs.

- **Exacerbation of Myasthenia Gravis:** Instruct patients to inform their physician of any history of myasthenia gravis. Instruct patients to notify their physician if they experience any symptoms of muscle weakness, including respiratory difficulties.
- **Hypersensitivity Reactions:** Inform patients that BAXDELA can cause hypersensitivity reactions, even following a single dose, and to discontinue BAXDELA at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (for example, swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction.
- **Diarrhea:** Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, instruct patients to contact their physician as soon as possible.
- **Antibacterial Resistance:** Inform patients that antibacterial drugs including BAXDELA Tablets and Injection should only be used to treat bacterial infections. They do not treat viral infections (for example, the common cold). When BAXDELA Tablets and BAXDELA Injection are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by BAXDELA Tablets and BAXDELA Injection or other antibacterial drugs in the future.

Administration with Food and Concomitant Medications

- Inform patients that BAXDELA Tablets may be taken with or without food and without any dietary restrictions [see *Dosage and Administration* (2.1) and *Clinical Pharmacology* (12.3)].
- Inform patients that BAXDELA Tablets should be taken at least 2 hours before or 6 hours after antacids containing magnesium, or aluminum, with sucralfate, with metal cations such as iron, or with multivitamin preparations containing zinc or iron, or with didanosine buffered tablets for oral suspension or the pediatric powder for oral solution.

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