Aminolevulinic Acid Hydrochloride (Gleolan)

**Manufacturer:** NX Development Corp., Lexington, Kentucky

**Date of Approval:** June 6, 2017

**Indication:** Gleolan is indicated in patients with glioma (suspected World Health Organization [WHO] grades III or IV on preoperative imaging) as an adjunct for the visualization of malignant tissue during surgery.

**Drug Class:** Imaging agent

**Uniqueness of Drug:** This is the first fluorescing optical imaging agent approved for use with gliomas. Gleolan is an oral solution that formerly received Food and Drug Administration orphan drug status.

**Warnings and Precautions:**

**Contraindications:** Do not use in patients with hypersensitivity to aminolevulinic acid (ALA) or porphyrins. Gleolan is potentially ineffective in individuals with acute or chronic types of porphyria.

**Phototoxic reactions:** Do not administer Gleolan with phototoxic drugs (St. John’s wort, griseofulvin, thiazide diuretics, sulfonlureas, phenothiazines, sulfonamides, quinolones, and tetracycline). Topical preparations containing ALA should not be administered for 24 hours during the perioperative period. Exposure to sunlight or interior lights should be reduced for 24 hours following surgery.

**Risk of misinterpretation:** Nonfluorescing tissue in the surgical field does not rule out the presence of tumor. Fluorescence may be seen in areas of inflammation or metastases from other tumor types.

**Hypersensitivity reactions:** Hypersensitivity reactions including serious events have occurred (anaphylactic shock, swelling, and urticaria).

**Adverse events (AEs):** Those occurring in more than 1% of patients in the week following surgery were hypotension, nausea, pyrexia, and vomiting. AEs that occurred within the first six weeks following surgery in less than 1% of patients included aphasia (8%), headache (2.7%), hemiparesis (7.8%), hemianopsia (3.2%), hemiplegia (1.9%), monoparesis (1.3%), hypoesthesia (1.1%), and seizure (1.9%). Brain edema occurred in less than 1% of patients within the first six weeks following surgery.

**Nervous system disorders:** Nervous system disorders occurred in 29% of patients within the first week following surgery. Those that occurred in more than 1% of patients included aphasia (8%), headache (2.7%), hemiparesis (7.8%), hemianopsia (3.2%), hemiplegia (1.9%), monoparesis (1.3%), hypoesthesia (1.1%), and seizure (1.9%). Brain edema occurred in less than 1% of patients within the first six weeks following surgery.

**Dosage and Administration:** The recommended dose of reconstituted Gleolan is 20 mg/kg of body weight (see full prescribing information). More than one vial may be required. Each vial should be mixed in 50 mL of liquid for drinking (measured with a volumetric device). Calculate the administration volume in milliliters, and administer orally three hours (range, two to four hours) prior to anesthesia induction. This agent must be used with a standard surgical operating microscope adapted with a blue-light-emitting light source and ancillary excitation and emission filters to visualize fluorescence excitation in the wavelength of 375 to 440 nm and for observation from 620 to 710 nm.

**Commentary:** The efficacy of Gleolan 20 mg/kg was evaluated in three clinical studies involving patients (18–75 years of age) who had preoperative magnetic resonance imaging (MRI) results compatible with high-grade glioma (WHO grade III or IV) and were undergoing surgical resection. Two trials were open-label and included patients with newly diagnosed high-grade glioma (n = 33) and recurrent high-grade glioma (n = 36). After initial debulking, biopsies were obtained under fluorescent light from fluorescent and nonfluorescent sites. Presence of fluorescence (positive/negative) was compared to tumor status (true/false) using histopathology as the reference. A third study was a randomized, multicenter study in patients (N = 415) with a preoperative diagnosis of high-grade glioma by MRI. In these three studies, Gleolan demonstrated high predictive value for visualization of malignant tissue as verified by histopathology of biopsied fluorescent tissue.

**Source:** NX Development Corp., Gleolan prescribing information

Delafloxacin (Baxdela)

**Manufacturer:** Melinta Therapeutics, Lincolnshire, Illinois

**Date of Approval:** June 19, 2017

**Indication:** Delafloxacin is indicated in adult patients for treating acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible isolates of the following:

- Gram-positive organisms: *Staphylococcus aureus* (including methicillin-resistant and methicillin-susceptible 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*.

**Drug Class:** Fluoroquinolone antibacterial

**Uniqueness of Drug:** Delafloxacin was given priority review by the Food and Drug Administration (FDA) due to its designation as a qualified infectious disease product. It is available for intravenous (IV) infusion or oral dosing (tablet).

**Warnings and Precautions:**

**Boxed warning:** serious adverse reactions, including tendinitis, tendon rupture, peripheral neuropathy, central nervous system effects, and exacerbation of
myasthenia gravis. Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including tendinitis and tendon rupture, peripheral neuropathy, and central nervous system effects. Delafloxacin should be immediately discontinued and avoided in patients who experience any of these serious adverse reactions. Fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis; avoid using delafloxacin in patients with a known history of this disease.

**Hypersensitivity reactions.** Serious and occasionally fatal anaphylactic reactions, some following the first dose, have been reported in patients receiving fluoroquinolone therapy. Reactions may occur after first or subsequent delafloxacin doses. At the first sign of a skin rash or any other sign of hypersensitivity, discontinue delafloxacin.

**Clostridium difficile–associated diarrhea (CDAD).** Patients should be evaluated if diarrhea occurs. 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.

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

**Hepatic/renal impairment.** No dosage adjustment is necessary in patients with hepatic impairment. In patients with mild (estimated glomerular filtration rate [eGFR] of 60–89 mL/min/1.73 m²) or moderate (eGFR of 30–59 mL/min/1.73 m²) renal impairment, no dosage adjustments are necessary. Dosing adjustments are required for IV infusion in patients with an eGFR less than 30 mL/min/1.73 m² (see full prescribing information). Delafloxacin is not recommended in patients with end-stage renal disease (eGFR less than 15 mL/min/1.73 m²).

**Dosage and Administration:** Delafloxacin may be administered by IV infusion (300 mg over 60 minutes every 12 hours) or via an oral tablet (450 mg every 12 hours) for a total duration of five to 14 days. The 450-mg tablet is bioequivalent to and interchangeable with the 300-mg IV dose, and can be given without regard to food. In patients with severe renal impairment (eGFR of 15–29 mL/min/1.73 m²), the IV delafloxacin dose should be decreased to 200 mg every 12 hours; the oral dose of delafloxacin in patients with severe renal impairment does not require adjustment.

**Commentary:** The efficacy of delafloxacin was assessed in two phase 3 studies in adult patients (N = 1,510) with ABSSSI that demonstrated that IV and oral delafloxacin monotherapy was statistically noninferior to the combination of vancomycin plus aztreonam. The FDA primary endpoint was early clinical response at 48–72 hours. The most common adverse events were cellulitis (39%), wound infection (35%), and major cutaneous abscess (25%). Delafloxacin was well tolerated with a 0.9% discontinuation rate due to adverse events. In this short-duration study, delafloxacin did not show any potential for QT prolongation or phototoxicity. There have been no signals of adverse effects on liver function, kidney function, or glucose regulation in controlled clinical studies. There are no anticipated drug–drug interactions with delafloxacin other than coadministration with chelating agents.

**Sources:** Melinta Therapeutics, Baxdela prescribing information.

**Glecaprevir/Pibrentasvir (Mavyret)**

**Manufacturer:** AbbVie, Inc., North Chicago, Illinois

**Date of Approval:** August 3, 2017

**Indication:** Mavyret, a fixed-dose combination of glecaprevir (a hepatitis C virus [HCV] NS3/4A protease inhibitor) and pibrentasvir (an HCV NS5A inhibitor), is indicated for treating patients with chronic HCV infection of genotypes (GT) 1–6 without cirrhosis and with compensated cirrhosis (Child–Pugh A). It is also indicated for the treatment of adults with HCV GT1 infection who were previously treated with a regimen containing an NS5A inhibitor or an NS3/4A protease inhibitor, but not both.

**Drug Class:** HCV antiviral

**Uniqueness of Drug:** Glecaprevir/pibrentasvir is the first eight-week regimen approved for all adult treatment-naïve HCV GT1–6 patients without cirrhosis. Previously, standard treatment was at least 12 weeks in duration. It is also a once-daily, non-ribavirin-based treatment. Prior to its approval, glecaprevir/pibrentasvir received breakthrough therapy and priority review designations from the Food and Drug Administration (FDA).

**Warnings and Precautions:**

**Boxed warning: risk of hepatitis B virus (HBV) reactivation in patients coinfected with HCV and HBV.** HBV reactivation has been reported with glecaprevir/pibrentasvir. Some cases resulted in fulminant hepatitis, hepatic failure, and death. All patients should be tested for evidence of current or prior HBV infection prior to initiating HCV treatment. Monitor HCV/HBV coinfected patients for HBV reactivation and hepatitis flare during HCV treatment and during post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

**Drug interactions.** Carbamazepine, efavirenz, and St. John’s wort may significantly decrease plasma concentrations of glecaprevir/pibrentasvir, leading to a reduced therapeutic effect of this HCV treatment. The use of these agents with glecaprevir/pibrentasvir is not recommended. There is a long list of clinically significant drug interactions. Consult the full prescribing information prior to initiating therapy.

**Hepatic/renal impairment:** Glecaprevir/pibrentasvir is not recommended in patients with moderate hepatic impairment (Child–Pugh B), and it is contraindicated in patients with severe hepatic impairment (Child–Pugh C). No adjustments are needed for renal impairment.

**Dosage and Administration:** The recommended dosage of glecaprevir/pibrentasvir is three tablets taken once daily with food. The tablets each contain 100 mg of glecaprevir and 40 mg of pibrentasvir.

The therapy duration for treatment-naïve patients with HCV GT1–6 without cirrhosis is eight weeks. Treatment-naïve patients with HCV GT1–6 with compensated cirrhosis (Child–Pugh A) should receive therapy for 12 weeks.

Treatment-experienced patients will require a regimen that is eight to 16 weeks in duration, dependent on the drugs contained in their previous regimen (see full prescribing information). continued on page 683
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Commentary: The safety and efficacy of glecaprevir/pibrentasvir were evaluated in nine clinical trials enrolling approximately 2,300 adults with all major HCV genotypes (GT1–6) and with mild or no cirrhosis. The treatment duration with glecaprevir/pibrentasvir differed depending on the patient’s treatment history, viral genotype, and cirrhosis status. Trial results demonstrated that 92% to 100% of patients treated with glecaprevir/pibrentasvir for eight, 12, or 16 weeks had an undetectable viral load 12 weeks after treatment completion. These results suggest that the patients’ infections had been cured. The most common adverse events in clinical trials were headache, fatigue, and nausea.

Sources: AbbVie, Inc., Mavyret prescribing information, FDA