CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208610Orig1s000
208611Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	208610 and 208611
PDUFA Goal Date	June 19, 2017
OSE RCM #	2016-2428; 2016-2440
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Acting Team Leader	Doris Auth, Pharm.D., Associate Director (Acting)
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	May 22, 2017
Subject	Review to determine if a REMS is necessary
Established Name	Delafloxacin Meglumine
Trade Name	Baxdela
Name of Applicant	Melinta Therapeutics Inc.
Therapeutic Class	Fluoroquinolone antibacterial agent
Formulation(s)	450 mg capsule (NDA 208610) and 300mg vial (NDA 208611)
Dosing Regimen	300 mg IV Q12h administered over 60 minutes by intravenous infusion or 450 mg oral Q12h at the discretion of the physician for a total duration of 5 to 14 days.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Baxdela (delafloxacin meglumine) is necessary to ensure the benefits outweigh its risks. Melinta Therapeutics Inc. submitted New Drug Applications (NDA) 208610 and 208611 for delafloxacin with the proposed indication 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*, (b) (4) *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group, (b) (4) (b) (4) *Streptococcus pyogenes*, and *Enterococcus faecalis*, and by the following Gram-negative organisms: *Escherichia coli*, *Enterobacter cloacae*, (b) (4) *Klebsiella pneumoniae*, (b) (4) and *Pseudomonas aeruginosa*. The common adverse events reported with delafloxacin are hypersensitivity reactions, diarrhea, and possible increase in hepatic transaminases. The applicant did not submit a REMS with this application. As with other fluoroquinolones antibiotics, the risks of serious adverse reactions including tendinitis, tendon rupture, peripheral neuropathy, central nervous system effects, and exacerbations of myasthenia gravis, will be included in the label as a Boxed Warning. The proposed label also includes a Medication Guide.

DRISK has determined that a REMS is not needed to ensure the benefits of delafloxacin outweigh its risks. Delafloxacin's efficacy was found to be non-inferior to comparator and provides evidence to support the efficacy of delafloxacin for the treatment of ABSSSI in adults. The risk of hypersensitivity reactions and *C. difficile*-associated diarrhea (CDAD) will be included in Warnings and Precautions of the label, while the adverse reactions of urticarial, diarrhea and hepatic transaminases elevations to address safety will be communicated in labeling in the Adverse Reactions section of the label.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Baxdela (delafloxacin meglumine) is necessary to ensure the benefits outweigh its risks. Melinta Therapeutics Inc. submitted New Drug Applications (NDA) 208610 and 208611 for delafloxacin with the proposed indication 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*, (b) (4) *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group, (b) (4) (b) (4) *Streptococcus pyogenes*, and *Enterococcus faecalis*, and by the following Gram-negative organisms: *Escherichia coli*, *Enterobacter cloacae*, (b) (4) *Klebsiella pneumoniae*, (b) (4) and *Pseudomonas aeruginosa*.[1] This application is under review in the Division of Anti-Infective Products (DAIP). The applicant did not submit a REMS with this application but proposed Prescribing Information that includes boxed warning, warnings and precautions and Medication Guide. The medical issues of interest for the fluoroquinolone class of antibiotics risks of serious adverse reactions including tendinitis, tendon rupture, peripheral neuropathy, central nervous system effects, and exacerbations of myasthenia gravis, will be included in the label as a Boxed Warning.

2 Background

2.1 PRODUCT INFORMATION

Delafloxacin, a new molecular entity, is an anionic fluoroquinolone antibiotic with a broad spectrum of antibacterial activity; proposed for indication as 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*, (b) (4) *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group, (b) (4) (b) (4) *Streptococcus pyogenes*, and *Enterococcus faecalis*, and by the following Gram-negative organisms: *Escherichia coli*, *Enterobacter cloacae*, (b) (4) *Klebsiella pneumoniae*, (b) (4) (b) (4) and *Pseudomonas aeruginosa*. Delafloxacin, like other members of the fluoroquinolone class, inhibits DNA synthesis by targeting bacterial DNA gyrase and topoisomerase IV.[2] Delafloxacin is supplied as 450 mg tablet and 300 mg lyophilized powder for intravenous (IV) injection. For treatment of adults with ABSSSI, the proposed regimen of delafloxacin is 300 mg IV Q12h administered over 60 minutes by intravenous infusion or 450 mg oral Q12h at the discretion of the physician for a total duration of 5 to 14 days.[a] Delafloxacin is a new molecular entity (NME) NDA type 505(b)(1) pathway application.[b] Delafloxacin was designated as a Qualified Infectious Disease Products (QIDP) and Fast Track with Priority review for the treatment of ABSSSI. Delafloxacin is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for delafloxacin (NDA 208610 and 208611) relevant to this review:

- 03/21/2007: Investigation New Drug (IND) 76096 submission was received.
- 09/08/2012: Qualified Infectious Disease Products (QIDP) designation request for delafloxacin was granted for the indications of acute bacterial skin and skin structure infections and community acquired bacterial pneumonia.
- 10/17/2012: Fast track designation granted
- 03/10/2016: FDA agreed with the applicants initial pediatric study plan and acknowledged the request for a full waiver for ABSSSI.
- 10/19/2016: NDA 208610 submission for delafloxacin tablet and NDA 208611 for delafloxacin injection with the proposed indication ABSSSI, received.
- 02/08/2017: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for delafloxacin.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Acute bacterial skin and skin-structure infections (ABSSSIs), formerly called complicated skin and skin-structure infection (cSSSIs) are among the most common infections encountered in clinical practice, both in community and hospital settings.[3,4] The 2013 FDA Guidance for Industry (Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment) defines an ABSSSI (also called cSSSI) as a bacterial infection of the skin with a lesion size area of at least 75 cm^2 (lesion size measured by the area of redness, edema, or induration). These infections are subdivided into the following categories: cellulitis/erysipelas, wound infection and major cutaneous abscess.[5] There is a wide clinical spectrum of ABSSSIs, from simple uncomplicated abscesses to life-threatening necrotizing fasciitis, and agreement upon severity classification is lacking.[6] Although the majority of patients receive care in the ED and are not admitted, complications due to ABSSSIs often lead to hospitalization. The true prevalence of SSTIs is unknown because mild infections are typically self-limiting and patients do not seek medical attention. It is not presently known how many revisits/admissions are represented among the over 600,000 to 800,000 documented admissions for ABSSSIs in the U.S. annually. [4,c] The continuing increase in antimicrobial resistance in U.S. hospitals remains a concern.[7] S. aureus infections are usually treated with methicillin-based antibiotics, but drug resistance has become increasingly common, with approximately 60% of inpatient infections thought to be methicillin resistant[7], thereby making these infections much more difficult to treat.[d]

3.2 Description of Current Treatment Options

Antimicrobial therapy is generally considered necessary for the treatment of ABSSSI.[8] Skin and soft-tissue infections (SSTIs) are an important cause of morbidity and mortality among hospitalized patients and a major therapeutic challenge for clinicians. Although uncomplicated SSTIs are managed successfully on an outpatient basis, more serious infections extending to the subcutaneous tissue, fascia, or muscle require complex management.[9] If specific pathogens are isolated in cultures, antimicrobial therapy can be tailored to the specific isolates; however, when patients with ABSSSI first present to health care practitioners, empiric therapy is required to initiate treatment. Most streptococci remain susceptible to penicillin and β-lactam antibiotics, providing many treatment options for adults once culture results are known. ABSSSIs caused by MRSA are becoming more common both within the hospital and in the community setting.[10] When MRSA is identified as a single pathogen, several treatment options exist in the US, including vancomycin, daptomycin, linezolid, tigecycline, tedizolid, telavancin, oritavancin, dalbavancin, and ceftaroline.[8]

Agents with Gram-positive and MRSA activity, such as linezolid, daptomycin and vancomycin, have been available for some time; however, these older agents, along with many of the agents more recently approved for ABSSSI, only provide Gram-positive coverage (see Table 1 in the Appendix). In certain clinical settings, a wider variety of potential pathogens, including Gram-negatives, may be present, such

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

that broader spectrum antibiotics or multiple antibiotics may be required.[8] Cephalosporins, carbapenems (meropenem, imipenem), and ureido-penicillins (such as piperacillin), aminoglycosides, or quinolone antibacterials can be used to provide Gram-negative coverage in these situations. In cases where MRSA and Gram-negative organisms are isolated, these agents can be added to MRSA active agents. Ceftaroline and tigecycline are active against Gram-negative organisms, but are only available in an IV formulation. Delafloxacin possesses both Gram-positive/MRSA activity and Gram-negative activity and, it offers the flexibility of fixed dose IV and oral treatment of ABSSSI. Inadequate treatment of MRSA due to antibiotic resistance is a factor in relapse of ABSSSI.[11] Newer and alternative treatment options, with their broad-spectrum activity against Gram-positive and Gram-negative organisms, are needed to treat these infections, and can be used as monotherapy.[12]

4 Benefit Assessment

The efficacy and safety of delafloxacin for the treatment of Acute Bacterial Skin and Skin Structure Infections was demonstrated in two phase 3 studies (RX-3341-302, and RX-3341-303). 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.

Study RX-3341-302 compared delafloxacin 300 mg. In study RX-3341-302, 660 patients with ABSSSI were randomized to receive delafloxacin 300 mg via intravenous infusion Q12h (n=331) or vancomycin plus aztreonam (n=329). In study RX-3341-303, 850 patients with ABSSSI were randomized to receive delafloxacin 300 mg via intravenous infusion Q12h for 6 doses then made a mandatory switch to oral delafloxacin 450 mg Q12h (n=423) or vancomycin plus aztreonam (n=427).

In both studies, Aztreonam therapy was discontinued if no gram-negative pathogens were identified in the baseline cultures. The primary endpoint of both Phase 3 studies, RX-3341-302 and RX-3341-303, was the objective clinical response rate at 48 to 72 hours post initiation of treatment, defined as a 20% or greater decrease in lesion size as determined by digital planimetry of the leading edge of erythema without other reasons for failure (use of another antibacterial or surgical procedure to treat for lack of efficacy). This endpoint is consistent with FDA ABSSSI Guidance.[5] A 2-sided 95% confidence interval (CI) for noninferiority testing was computed based on the difference in sample responder rates for vancomycin + aztreonam and delafloxacin at 48 to 72 hours (± 2 hours) after initiation of treatment using a nonstratified method. If the lower limit of the 2-sided 95% CI was ≥ −0.10, it was concluded that delafloxacin was noninferior to vancomycin + aztreonam for treating patients with ABSSSI. The Intent-to-Treat (ITT) patient population included all randomized patients. Missing patients were treated as failures in the ITT analysis set.

All patients treated with delafloxacin had 2 or more systemic signs of infection in both studies, and 55% vs 58% of patients had 3 or more systemic signs of infection, defined as lymphadenopathy, fever, lymphadenitis, purulent drainage, elevated CRP or WBC count in study RX-3341-302 vs in study RX-3341-303, respectively.

Both studies met the primary objective of demonstrating that delafloxacin is non-inferior to control[e]; findings from the primary analyses of these studies are presented in Table 2.[13] For Study RX-3341-302, a

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

lower clinical response rate is observed in delafloxacin patients (78.2%) compared to control patients (80.9%) with a treatment effect estimate of -2.6% and 95% CI (-8.8%, 3.6%). In Study RX-3341-303, the observed clinical response rate is higher in delafloxacin patients (83.7%) compared to control patients (80.6%) with a treatment effect estimate of 3.1% and corresponding 95% CI (-2.0%, 8.3%). As shown in this table, the percentage of patients with missing primary outcome data, i.e. patients who did not have an efficacy evaluation within the first 3 days of study, appears somewhat high in both studies (approximately 7% in Study RX-3341-302 and 5% in Study RX-3341-303). Sensitivity analyses to assess the impact of missing data yields consistent findings with the primary analysis.

Table 2: Primary Analysis Findings (Objective Clinical Response at 48 to 72 hours) – ITT Population[13]

	Study RX-3341-302		**Study RX-3341-303**	
	Delafloxacin (300 mg IV) N=331	**Vancomycin 15 mg/kg + Aztreonam N=329**	**Delafloxacin (300 mg IV & 450mg Oral) N=423**	**Vancomycin 15 mg/kg + Aztreonam N=427**
Clinical Response*, n (%)	259 (78.2)	266 (80.9)	354 (83.7)	344 (80.6)
Clinical Failure**, n (%)	46 (13.9)	41 (12.4)	49 (11.6)	62 (14.5)
Missing***, n (%)	26 (7.9)	22 (6.7)	20 (4.7)	21 (4.9)
Difference (95% CI)	-2.6 (-8.8, 3.6)		3.1 (-2.0, 8.3)	

*Difference in clinical response rates, expressed as percentages, based on Miettinen and Nuriminen without stratification.
**Response is classified as failure for any of the following reasons: <20% reduction of ABSSSI lesion spread of erythema area as determined by digital measurements of the leading edge, administration of rescue antibacterial drug therapy or administration of non-study antibacterial drug therapy for treatment of ABSSSI before the primary efficacy assessment, need for unplanned surgical intervention except for limited bedside debridement and standard wound care before the primary endpoint assessment, or death by 74 hours after initiation of study drug.
***Missing comprises patients who did not have a measurement reported at the primary evaluation time point; considered as failures in the primary analysis.

A key secondary endpoint analyzed in this review is investigator-assessed response which is evaluated at follow-up visit occurring on Day 14 and at late follow-up visit occurring between Day 21 to 28. Response for this endpoint was defined in two ways in the study protocols; firstly as cure, i.e. complete resolution of signs and symptoms of ABSSSI, and secondly as success, i.e. cure or improvement in signs and symptoms with no additional therapy needed. Similar cure rates and success rates are observed across the delafloxacin and control arms for both studies. The cure rates at the follow-up visit are 52% v. 50.5% in Study 302 and 57.7% v. 59.7% in Study 303 for delafloxacin and control arms, respectively. Higher success rates at the follow-up visit are observed: 81.6% v. 83.3% in Study 302 and 87.2% v. 84.8% in Study 303 for delafloxacin and control arms, respectively.

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 delafloxacin application is still under review, please refer to Dr. Caroline Jjingo's review for the full clinical review of efficacy and safety.

5 Risk Assessment

At the time of this writing, labeling negotiations were still ongoing with the applicant. The following section is a summary of relevant safety information to date for delafloxacin.

The safety concerns with delafloxacin are the risks of serious adverse reactions associated with other fluoroquinolones antibiotics including tendinitis, tendon rupture, peripheral neuropathy, central nervous system effects, and exacerbations of myasthenia gravis. If approved, labeling will be consistent with other fluoroquinolones and these risks will be included as Boxed Warnings. Fluoroquinolones have historically been associated with a number of well-described risks requiring labeling updates including a description of musculoskeletal, cardiac, dermatologic, neurologic, and neuro-psychiatric risks.[14,f] Historical knowledge of the safety of fluoroquinolones allows for a prospective assessment of Adverse Events of Special Interest (AESIs) in the development of a new fluoroquinolone such as delafloxacin. The assessment focuses on the AESIs of potential myopathy, *C. difficile* diarrhea, convulsions, potential peripheral neuropathy, potential tendon disorder, potential QT prolongation, potential phototoxicity, potential allergic reactions, potential dysglycemias (hyperglycemia, hypoglycemia), and hepatic-related events. It was noted that fewer patients in the delafloxacin group had AESIs than in the comparator group (11.1% and 14.2%, respectively).

The most common treatment emerging adverse events (TEAE) reported in the studies are gastrointestinal in nature (i.e. diarrhea, nausea, and vomiting). The overall safety evaluation of delafloxacin is based on data from741 patients treated with delafloxacin and 751 patients treated with comparator antibacterial drugs in Phase 3 ABSSSI clinical trials (RX-3341-302 and RX-3341-303). Adverse drug reactions reported in > 2% of subjects in the Phase 3 ABSSSI population treated with delafloxacin were diarrhea, nausea, headache, transaminase elevations, vomiting and infusion site reactions (see table 3).

Table 3: Selected Adverse Reactions Occurring ≥ 2% in ABSSSI Phase 3 Clinical Trials[1]

	Delafloxacin N = 741 (%)	**Vancomycin/aztreonam N = 751 (%)**
Diarrhea	8%	3%
Nausea	8%	6%
Vomiting	2%	2%
Headache	3%	6%
Transaminase Elevations*	3%	4%
Infusion Site Reactions†	9%	10%

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

† Pooled reports include such terms as: infusion site bruise, discomfort, edema, erythema, extravasation, irritation, pain, phlebitis, or swelling.

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

The integration of safety data for the delafloxacin 300-mg IV/450-mg oral doses across the 4 controlled, 2 clinical studies each in Phase 2 and 3 studies (RX-3341-201, RX-3341-202, RX-3341-302, and RX-3341-303) allows for a comprehensive assessment of the safety profile of IV and oral delafloxacin in support of the treatment of patients with ABSSSI. The Multiple-Dose ABSSSI analysis set includes 1840 subjects with ABSSSI who received multiple doses of delafloxacin in the 300-mg IV/450-mg oral delafloxacin Q12h treatment arms in the 4 controlled studies.

Diarrhea:

The statistical reviewer stated that there may an increased risk of diarrhea with delafloxacin based on an exploratory analysis drawn from Study 302 and Study 303, in which a risk difference of 4.8% is obtained with corresponding 95% CI (2.5%, 7.1%) compared to comparator. However, there is a larger observed difference (4% to 5%) in the incidence of diarrhea in delafloxacin patients compared to control patients across both studies. However, caution is advised in drawing definitive conclusions regarding the significance of this finding.[13] In multiple-dose ABSSSI analysis set, diarrhea AEs occurred in higher proportion of patients in the delafloxacin arm (8.6%) compared with comparators (3.9%), and treatment-related diarrhea AEs occurred in delafloxacin arm (6.9%) compared with comparators (2.5%).

Two patients (0.2%) in the delafloxacin group had *C. difficile* diarrhea compared with none in the comparator group. One of these patients entered the study as a prior treatment failure with previous treatment with Bactrim (sulfamethoxazole/trimethoprim) and clindamycin. Neither patient had *C. difficile* diarrhea lasting longer than 30 days. In both patients, the events of diarrhea were considered related to treatment and of mild severity. No treatment discontinuations or SAEs were attributed to *C. difficile* diarrhea in patients treated with delafloxacin.

The adverse reaction of diarrhea will be communicated in labeling in the Adverse Reactions section of the label. Similar to other drugs in this class, the risk of *C. difficile*-associated diarrhea (CDAD) will be included in Warnings and Precautions of the label.

Deaths:

There were a total of 4 TEAEs leading to death, 1 in the delafloxacin group (septic shock) and 3 in the comparator group (myocardial infarction, intestinal ischemia, and pulmonary embolism), all of which were unrelated to treatment. The death in the delafloxacin arm was assessed as unrelated to study treatment by the investigator. The applicant's medical monitor agreed with investigator assessment of causality; the patient's complicated medical history provided confounding factors for this outcome.[15]

Adverse Reactions Leading to Discontinuation:

Delafloxacin was discontinued due to an adverse reaction in 8/741 (1.1%) patients and the comparator was discontinued due to an adverse reaction in 20/751 (2.7%) patients. The most commonly reported adverse reactions leading to study discontinuation in the delafloxacin arm included urticaria (2/741; 0.3%), hypersensitivity (2/741; 0.3%), infusion site extravasation (1/741; 0.1%), pulmonary embolus (1/741; 0.1%), vomiting (1/741; 0.1%)and allergic dermatitis (1/741; 0.1%); 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, infusion site extravasation and pruritus

(2/751; 0.3%), liver function test abnormal, hypoglycemia, muscle spasms, convulsions, renal failure acute, and erythema (1/741; 0.1%).[g]

Hypersensitivity reactions:

Hypersensitivity reactions have been reported in patients receiving delafloxacin. These reactions may occur after first or subsequent doses of delafloxacin. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving fluoroquinolone antibacterial drugs.

The risk of hypersensitivity reactions will be included in Warnings and Precautions of the label, while the adverse reaction of urticaria to address safety will be communicated in labeling in the Adverse Reactions section of the label.

Hepatic transaminases elevations:

Rates of hepatic events in the hepatic Standardized MedDRA query (SMQ) were similar between patients in the delafloxacin and comparator groups (3.2% and 3.4%, respectively). Fewer patients had hepatic AESIs lasting longer than 30 days in the delafloxacin group versus the comparator group (0.7% and 1.0%, respectively). Rates of treatment-related hepatic events were similar between patients in the delafloxacin and comparator groups (2.3% and 2.4%, respectively). There were no premature discontinuations from delafloxacin due to a hepatic event. One delafloxacin-treated patient experienced the SAE of increased ALT/AST. The patient who was attributed to ALT/AST elevations was known to be on concomitant methamphetamine, heroin, and morphine sulfate at first dose of study drug. Baseline hepatitis C antibody testing was negative and confirmed positive on Day 73. The investigator considered the ALT and AST events possibly related to study drug. The applicant's medical monitor considered the ALT and AST events unlikely related to study drug and likely related to hepatitis C. The investigator assessed the clinical response at the End-of Treatment, Follow-up, and Late Follow-up Visits as improved for all 3 visits. There were no patients who fit the definition of Hy's law.

The adverse reaction of increase in hepatic transaminases to address safety will likely be communicated in labeling in the Adverse Reactions section of the label.

Pulmonary embolism:

There were two reported events of pulmonary embolism in Study RX-3341-303. The investigator considered both events of pulmonary embolism as unrelated to study drug. The investigator assessed the clinical response at the End-of-Treatment Visit, Follow-up Visit, and Late Follow-up Visit as improved for all 3 visits. The adverse reaction of pulmonary embolism to address safety will likely be communicated in labeling in the Adverse Reactions section of the label.

Renal Impairment:

The use of delafloxacin (IV and oral) in patients with ESRD may not be appropriate as the risk of extensive accumulation of sulfobutylether-β-cyclodextrin (SBECD) in patients with ESRD receiving IV delafloxacin is unknown. SBECD is a cyclodextrin excipient used to improve drug solubility, stability, and

[g] Jjingo, C. to Olickal, T. (E-mail communication from clinical reviewer to DRISK), dated May 9, 2017.

bioavailability. The potential risk of nephrotoxicity caused by SBECD has been identified in animal studies, specifically cytoplasmic vacuolation in the epithelium of the renal tubules, renal pelvis and urinary bladder.[16] The impact of ESRD on delafloxacin disposition following oral dosing is unknown as no observed data are available in patients with ESRD receiving oral delafloxacin. In the renal impairment study, delafloxacin was administered within one hour after completion of a hemodialysis session; therefore delafloxacin exposure in subjects on an off-dialysis day has not been evaluated.[17]

6 Expected Postmarket Use

According to the current proposed indication, if approved, delafloxacin will be used both in outpatient and inpatient settings and will be prescribed by various types of healthcare providers such as general practice physicians, internal medicine physicians, midlevel practitioners, and Infectious Disease Specialists. The IV route or IV switch to oral route will be used in inpatient and/or outpatient settings such as infusion centers or home infusion.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for delafloxacin beyond routine pharmacovigilance and labeling. The applicant proposes a Boxed Warning in the labeling and a Medication Guide as part of labeling to inform patients regarding the potential risk of tendinitis, peripheral neuropathy, central nervous system effects, and worsening of myasthenia gravis.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for delafloxacin, DRISK considers patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and prescribing population. Delafloxacin is an anionic fluoroquinolone antibiotic with a broad spectrum of antibacterial activity. This drug is proposed for use in the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by caused by several gram-positive organisms and gram-negative organisms. Both studies (RX-3341-302 and RX-3341-303) met the primary objective clinical response rate at 48 to 72 hours post initiation of treatment, defined as a 20% or greater decrease in lesion size; demonstrating that delafloxacin is non-inferior to control. A key secondary endpoint, which was defined first as cure, i.e. complete resolution of signs and symptoms of ABSSSI, and second as success, i.e. cure or improvement in signs and symptoms with no additional therapy needed were also analyzed. Similar cure rates and success rates are observed across the delafloxacin and control arms for both studies. The cure rates at the follow-up visit are 52% v. 50.5% in Study 302 and 57.7% v. 59.7% in Study 303 for delafloxacin and control arms, respectively. Higher success rates at the follow-up visit are observed: 81.6% v. 83.3% in Study 302 and 87.2% v. 84.8% in Study 303 for delafloxacin and control arms, respectively.

In conclusion, delafloxacin was well-tolerated in the Phase 2 and Phase 3 ABSSSI studies. Fewer patients had TEAEs in the delafloxacin group versus the comparator group (47.7% and 52.4%, respectively). Most TEAEs were mild or moderate in severity and generally did not lead to treatment discontinuation. Discontinuations due to treatment-related AEs were 0.7% in the delafloxacin group compared to 2.4% in the comparator treatment group. The incidence of SAEs was similar between treatment groups. There

were a total of 4 TEAEs leading to death, 1 in the delafloxacin group and 3 in the comparator group, all of which were unrelated to treatment. It was noted that fewer patients in the delafloxacin group had AESIs than in the comparator group (11.1% and 14.2%, respectively). The medical issues of interest for the fluoroquinolone class of antibiotics risks of serious adverse reactions including tendinitis, tendon rupture, peripheral neuropathy, central nervous system effects, and exacerbations of myasthenia gravis, will be included in the label as a boxed warning.

The incidence of TEAEs in Study 302 and Study 303 appear generally consistent with other approved products for ABSSSI (see Table 1 in the Appendix). However, there is a larger observed difference (4% to 5%) in the incidence of diarrhea in delafloxacin patients compared to control patients across both studies. The statistical reviewer acknowledges that C. difficile-associated diarrhea (CDAD) has been reported with treatment of antibacterial agents, but there appears to be only one patient (a delafloxacin patient in Study 303) reported to have CDAD across both of the delafloxacin Phase 3 studies, and total of 2 patients (0.2%) across Phase 2 and Phase 3 studies. Findings for an exploratory analysis, result in an overall (common) risk difference of 4.8% with 95% CI (2.5%, 7.1%). This is suggestive of an increased risk of diarrhea with delafloxacin compared to control. The statistical reviewer notes that these studies were not designed for drawing conclusive statistical inference about safety outcomes; as such, caution is advised when interpreting the significance of this finding.

The concerning adverse reactions associated with delafloxacin appear to be hypersensitivity reactions, diarrhea, and possible increase in hepatic transaminases. The risk of hypersensitivity reactions and *C. difficile*-associated diarrhea (CDAD) will be included in Warnings and Precautions of the label, while the adverse reactions of urticarial, diarrhea and hepatic transaminases elevations to address safety will be communicated in labeling in the Adverse Reactions section of the label. Other fluoroquinolone antibacterial drugs with similar warnings and administered under similar inpatient and outpatient scenarios do not have a REMS requirement. The Boxed Warning is sufficient for risk mitigation for medical issues of interest for the fluoroquinolone class of antibiotics.

The clinical review of the delafloxacin application is still under review. DRISK believes that if approved, a REMS is not necessary at this time, for delafloxacin to ensure the benefits outweigh the risks for the following reasons: Delafloxacin's efficacy was found to be non-inferior to comparator and provide evidence to support the efficacy of delafloxacin for the treatment of ABSSSI in adults.[13] Despite the availability of many antibacterial agents approved for ABSSSI, have only provided Gram-positive coverage; a wider variety of potential pathogens, including Gram-negatives, may be required to treat with a broader spectrum antibiotics or multiple antibiotics. Delafloxacin could provide an alternative treatment options as broad spectrum coverage for patients with ABSSSI, as it possesses both Gram-positive/MRSA activity and Gram-negative activity and, it offers the flexibility of fixed dose IV and oral treatment of ABSSSI. Currently there are 5 different fluoroquinolones that are approved for systemic use in the United States includes ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, and ofloxacin. These approved fluoroquinolones do not have REMS. Labeling including a boxed warning, warnings and precautions, Medication Guide, routine pharmacovigilance, and post-marketing requirements will be used to communicate the safety issues associated with delafloxacin.

9 Conclusion & Recommendations

If approved, DRISK has determined that a REMS is not necessary to ensure the benefits outweigh the risks. Similar to other antibiotics in the class, fluoroquinolones, the risks will be communicated through

labeling including boxed warning, warnings and precautions, Medication Guide, routine pharmacovigilance, and post-marketing requirements. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Materials Reviewed

The following is a list of materials informing this review:

1. Melinta Therapeutics Inc. Summary of Clinical Safety for for Delafloxacin, dated October 19, 2016.

11 Appendices

11.1 TABLE 1: SUMMARY OF TREATMENT OPTIONS RELEVANT TO PROPOSED INDICATION[8]

Trade Name (Generic)	Approved year	Indication	Dosing/ Administration	Boxed Warning/Warnings and Precautions	REMS
MRSA SSTI					
Orbactiv[18] (Oritavancin)	2014	Indicated for the treatment of adult patients with acute bacterial skin and skin structure infections caused or suspected to be caused by susceptible isolates of designated Gram-positive microorganisms.	1200 mg single dose treatment administered by intravenous infusion over 3 hours.	Coagulation test interference, Hypersensitivity, Infusion-related reactions, *Clostridium difficile*-associated colitis, Concomitant use of warfarin: ORBACTIV may increase warfarin levels, Osteomyelitis.	No REMS
Dalvance[19] (Dalbavancin)	2014	Indicated for acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible strains of Gram-positive microorganisms.	Single Dose Regimen: 1500 mg Two-Dose Regimen: 1000 mg followed one week later by 500 mg	Serious hypersensitivity (anaphylactic) and skin reactions, Rapid intravenous infusion can cause reactions, ALT elevations, *Clostridium difficile*-associated diarrhea (CDAD)	No REMS
Vibativ[20] (Telavancin)	2009	Complicated skin and skin structure infections (cSSSI)	10 mg/kg by IV infusion over 60 minutes every 24 hours for 7 to 14 days	**Boxed Warning** for increased mortality in HABP/VABP patients with pre-existing moderate or severe renal impairment, nephrotoxicity, potential adverse developmental outcomes; Decreased efficacy among patients treated for skin and skin structure infections with moderate/severe pre-existing renal impairment, Coagulation test interference, Hypersensitivity reactions, Infusion-related reactions, *Clostridium difficile*-associated disease, QTc prolongation	REMS with MG & CP

Vancomycin[21]	1993	Indicated for the treatment of serious or severe infections caused by susceptible strains of methicillin-resistant (beta-lactam-resistant) staphylococci. It's effectiveness has been documented in other infections due to staphylococci, including septicemia, bone infections, lower respiratory tract infections, and skin and skin-structure infections.	30 mg/kg/d in 2 divided doses IV	Infusion reactions, nephrotoxicity, ototoxicity, *Clostridium difficile* associated diarrhea (CDAD)	No REMS
Zyvox[22] (Linezolid)	2000	Indicated in adults and children for the treatment of the following infections caused by susceptible Gram-positive bacteria: Nosocomial pneumonia; Community-acquired pneumonia; Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis; Uncomplicated skin and skin structure infections; Vancomycin-resistant *Enterococcus faecium* infections.	600 mg intravenous or oral every 12 hours for 10 to 14 days	Myelosuppression, peripheral and optic neuropathy, serotonin syndrome, *Clostridium difficile* associated diarrhea, hypoglycemia, potential interactions producing elevation of blood pressure	No REMS
Clindamycin[23]	1989	Skin and skin structure infections caused by *Streptococcus pyogenes, Staphylococcus aureus*, and anaerobes.	600 mg every 8 h IV or 300–450 mg qid po	Boxed Warning for *Clostridium difficile* associated diarrhea; Anaphylactic shock and anaphylactic reactions, benzyl alcohol toxicity in pediatric patients (Gasping Syndrome), Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in the treatment of meningitis.	No REMS
Cubicin[24] (Daptomycin)	2003	Complicated skin and skin structure infections (cSSSI)	4 mg/kg once every 24 hours for 7 to 14 days	Anaphylaxis/hypersensitivity reactions, myopathy and rhabdomyolysis, eosinophilic pneumonia, peripheral neuropathy, Potential nervous system and/or muscular system effects in pediatric patients younger than 12 months, *Clostridium difficile* associated diarrhea, persisting or relapsing *S. aureus* bacteremia/endocarditis, decreased efficacy was observed in patients with moderate baseline renal impairment.	No REMS
Teflaro[25] (Ceftaroline)	2010	Acute bacterial skin and skin structure infections (ABSSSI)	600 mg every 12 hours by IV infusion administered over 5 to 60 min	Serious hypersensitivity (anaphylactic) reactions, *Clostridium difficile* associated diarrhea (CDAD), direct Coombs' test seroconversion has been reported	No REMS

Doxycycline	1967	Skin and soft tissue infections due to MSSA or MRSA	100 mg bid po	The use of drugs of tetracycline class during tooth development may cause permanent discoloration of the teeth, *Clostridium difficile* associated diarrhea (CDAD)	No REMS
Trimethoprimsulfamethoxazole	1973	Skin and soft tissue infections due to MSSA or MRSA	1–2 doublestrength tablets bid po	Embryofetal toxicity, hypersensitivity and other fatal reactions, thrombocytopenia, Streptococcal infections and rheumatic fever, *Clostridium difficile* associated diarrhea, Treatment failure and excess mortality were observed in adjunctive treatment with Leucovorin for Pneumocystis jiroveci pneumonia	No REMS

12 References

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[15] Melinta Therapeutics Inc. Summary of Clinical Safety for for Delafloxacin, dated October 19, 2016.

[16] Wu K, Yan Z, Zhuang L, Florian J, Ramamoorthy A, Grimstein C. Office of Clinical Pharmacology Review for NDA 208610 & 208611 delafloxacin, dated March 28, 2017.

[17] FDA Late-Cycle Meeting Background Package, dated March 24, 2017.

[18] Orbactiv. Prescribing Information (last updated 10/2016).

[19] Dalvance. Prescribing Information (last updated 01/2016).

[20] Vibativ. Prescribing Information (last updated 05/2016).

[21] Vancomycin. Prescribing Information (last updated 01/2017).

[22] Zyvox. Prescribing Information (last updated 01/2015).

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[25] Teflaro. Prescribing Information (last updated 05/2016).

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