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APPLICATION NUMBER:

208610Orig1s000

208611Orig1s000

OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	John Farley, MD, MPH
Subject	Deputy Office Director Decisional Memo
NDA/BLA #	NDA 208610 and 208611
Supplement #	
Applicant Name	Melinta Therapeutics, Inc.
Date of Submission	October 19, 2016
PDUFA Goal Date	June 19, 2017
Proprietary Name / Established (USAN) Name	Baxdela /delafloxacin
Dosage Forms / Strength	Powder for injection, 300 mg/vial and tablets, 450 mg
Applicant Proposed Indication(s)/Populations	Acute bacterial skin and skin structure infections in adults
Action:	Approval
Approved Indication(s)/Populations (if applicable)	Acute bacterial skin and skin structure infections in adults

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Caroline Jjingo MD MPH
Statistical Review	Janelle Charles PhD
Pharmacology Toxicology Review	Amy Nostrandt DVM PhD and Wendelyn Schmidt, PhD
OPQ ATL Review	Balajee Shanmugam PhD
Microbiology Review	Jalal Sheikh PhD
Clinical Pharmacology Review	Kunyi Wu, PharmD
OPDP	Puja Shah PharmD
OSI	Bei Yu PhD
CDTL Review	Thomas Smith MD
OSE/DMEPA	Sevan Kolejian PharmD
OSE/DRISK	Till Olickal PharmD
DMPP	Twanda Scales BSN, MSN/Ed

OND=Office of New Drugs
 OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader
 OSE= Office of Surveillance and Epidemiology
 DEPI= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management
 DMPP=Division of Medical Policy Programs

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

I concur with the Benefit-Risk Assessment written by the Division Director and include it here with my additional summary comments.

The Applicant has provided adequate evidence to support the safety and efficacy of delafloxacin for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSI), at a dose of 300 mg every 12h administered over 60 minutes via intravenous infusion or 450 mg orally every 12h for a total duration of 5 to 14 days. The efficacy of delafloxacin was demonstrated in two adequate and well-controlled noninferiority trials comparing delafloxacin to vancomycin plus aztreonam. The key characteristics of the two trials were consistent with the recommendations in the ABSSSI guidance, including infection type, lesion size, use of prior effective antibacterial drugs, and endpoints.¹ Noninferiority was demonstrated in both trials for the primary endpoint of a 20% reduction in lesion size at the 48-72 hour timepoint post-randomization; the pre-specified noninferiority margin of 10% was met in both trials. Treatment effect was also seen at later time points including the end of therapy and the follow up visits.

While other approved therapies are available for the treatment of ABSSSI, it is preferable to have different therapeutic options. Resistance to available therapies is continuing to increase and hence having a variety of treatment options is always optimal. Also, it is important to have antibacterial drugs with different safety profiles to ensure that patients who are allergic or have safety issues with certain drugs or classes of drugs have treatment options. There are other approved therapies for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA), an important cause of ABSSSI; however, there are only few oral treatment options for patients with infections due to MRSA. As the spectrum of activity of delafloxacin includes MRSA and certain Gram-negative bacteria, it provides another oral option for patients for the treatment of ABSSSI.

From a safety standpoint, no significant safety concerns emerged in the safety database of 1682 delafloxacin-exposed subjects (varying doses and durations) that included 741 patients in the two Phase 3 trials. The common adverse reactions reported in the clinical trials included nausea, diarrhea, headache, transaminase elevations and vomiting. As delafloxacin is a member of the fluoroquinolone class of antibacterial drugs, it is possible that safety findings related to the drug will become evident postmarketing when a larger number of patients are exposed to the drug. Labeling for this product will include safety-related information that is applicable to the fluoroquinolone class of antibacterial drugs. Safety information regarding myasthenia gravis and disabling and potentially irreversible serious adverse reactions that have occurred together, including, tendinitis and tendon rupture, peripheral neuropathy, and central nervous system effects will be included in the Boxed Warning. The

¹ FDA guidance for industry *Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment* (October, 2013)
Deputy Office Director Memo NDAs 208610 and 208611 June 19, 2017

Warnings and Precautions section will include class labeling language including, disabling and potentially irreversible serious adverse reactions, tendinitis and tendon rupture, peripheral neuropathy, central nervous system effects, exacerbation of myasthenia gravis, and hypersensitivity reactions. Also, consistent with other fluoroquinolones, labeling will include a Medication Guide to convey important safety information to patients. Delafloxacin is not recommended in patients with End Stage Renal Disease (ESRD) (eGFR <15 mL/min including hemodialysis) as there are no observed data in patients with ESRD receiving delafloxacin tablets, and there are concerns with accumulation of the excipient sulfobutylether-beta-cyclodextrin (SBECD) in ESRD patients receiving the intravenous formulation. Continued pharmacovigilance postmarketing will help identify any emerging safety signals once the product is approved and used more widely.

Pediatric studies were waived as the risks with fluoroquinolones outweigh the benefits for the indication of ABSSSI. This information will be included in the Pediatric Use section of the prescribing information.

In summary, the overall Benefit-Risk is favorable. Substantial evidence of efficacy from two adequate and well-controlled trials has been provided in these NDAs and delafloxacin is safe for use under the conditions recommended in labeling. There are no concerns with product quality or other concerns that preclude approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	ABSSSI is a serious bacterial infection and includes conditions such as cellulitis, wound infections and abscesses.	ABSSSI is a serious bacterial infection that if left untreated can cause significant morbidity and lead to death in some circumstances.
Current Treatment Options	There are many approved antibacterial drugs for the treatment of ABSSSI or complicated skin and skin structure infections. Some of these drugs are available only as intravenous formulations and some are available as both oral and intravenous formulations. Most approved therapies cover the common Gram-positive bacteria that cause ABSSSI, including <i>S. aureus</i> and <i>Streptococcus pyogenes</i> . Some approved therapies are more broad-spectrum and have activity against Gram-negative bacteria as well. Approved antibacterial drugs including, linezolid, daptomycin, telavancin, ceftaroline, dalbavancin, tedizolid, and oritavancin also have activity against MRSA. Of these	There are many approved antibacterial drugs for the treatment of ABSSSI/complicated skin and skin structure infections. Approved therapies are available as either intravenous or intravenous and oral formulations.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	only linezolid and tedizolid are available in oral formulations.	
Benefit	<p>The efficacy of delafloxacin in the treatment of ABSSSI has been demonstrated in two adequate and well-controlled NI trials in which delafloxacin was noninferior to the comparator (vancomycin plus aztreonam) in the intent to treat population. The efficacy of delafloxacin was demonstrated for the primary endpoint of clinical response assessed at 48-72 hours from treatment initiation. Clinical response was also sustained at later time points including the end of therapy and at follow up on Day 14 ± 1. Efficacy findings were consistent across different analysis populations and in different subgroups. Patients enrolled in these trials had a variety of skin infections, including abscesses, wound infections, and cellulitis. The etiologic agents also varied and included the common Gram positive organisms (e.g., MSSA, MRSA, <i>S. pyogenes</i>) and Gram-negative bacteria (e.g. <i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i>). No specific concerns with regard to efficacy were noted for any of the organisms for which the product will be indicated.</p>	<p>Delafloxacin was demonstrated to be noninferior to an acceptable comparator regimen in two adequate and well-controlled trials. Delafloxacin offers the advantage of being available as parenteral and oral formulation and so patients do not need to be switched to a different therapy for oral step-down. It also provides for another oral treatment option for MRSA and can also be useful for the treatment of mixed infections due to its activity against the common Gram-positive and Gram-negative bacteria that cause ABSSSI.</p>
Risk	<p>The clinical development program for delafloxacin includes healthy volunteers and patients exposed to varying doses and durations of treatment. The safety database at the proposed dose and duration (oral/intravenous) in the Phase 3 trials was 741. The common adverse reactions reported in the clinical trials included nausea, diarrhea, headache, transaminase elevations and vomiting. As delafloxacin is a member of the fluoroquinolone class of antibacterial drugs, it is likely that safety findings related to this drug class will become evident postmarketing when a larger number of patients are exposed to the drug.</p>	<p>As delafloxacin is a member of the fluoroquinolone class of antibacterial drugs, there are safety concerns that should be taken into consideration. Although no major safety signals were identified in the database so far, it is important to note that the safety database at this time is rather small. As with other fluoroquinolones, it is likely that the safety signals will emerge postmarketing and will need to be closely monitored.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Risk Management</p>	<p>Labeling for this product will include safety-related information that is applicable to the fluoroquinolone class of antibacterial drugs. Safety information regarding myasthenia gravis and disabling and potentially irreversible serious adverse reactions that have occurred together, including, tendinitis and tendon rupture, peripheral neuropathy, and central nervous system effects will be included in the Boxed Warning. The Warnings and Precautions section will include class labeling language including, disabling and potentially irreversible serious adverse reactions, tendinitis and tendon rupture, peripheral neuropathy, central nervous system effects, exacerbation of myasthenia gravis, and hypersensitivity reactions. Also, consistent with other fluoroquinolones, labeling will include a Medication Guide to convey important safety information to patients. Continued pharmacovigilance postmarketing will help identify an emerging safety signals once the product is approved and used more widely.</p>	<p>Routine postmarketing surveillance activities will suffice at this point. There are no safety signals/potential for safety issues that require a Risk Evaluation and Mitigation Strategy (REMS) at this time. Labeling for the product, including the Medication Guide adequately conveys the safety concerns.</p>

2. Further discussion to support regulatory action

Background

Melinta Therapeutics, Inc. has submitted NDAs 208610 and 208611, for delafloxacin, a new fluoroquinolone antibacterial drug for the treatment of acute bacterial skin and skin structure infections (ABSSSI). During clinical development, Special Protocol Agreements had been reached for the IV-only trial (RX-3341-302) and the IV-to-oral trial (RX-3341-303), the adequate and well-controlled trials subsequently submitted to these NDAs. Qualified Infectious Disease Product (QIDP) designation was granted for the ABSSSI indication as well as Fast Track designation. Based on the QIDP designation, the NDAs received a priority review.

Product Quality

The Product Quality review team recommended approval from the Product Quality perspective, and I concur with their recommendation. Drug substance specifications, drug product specifications, and manufacturing facilities were deemed acceptable.

The outstanding Product Quality issues were assessed by the review team as low-risk and not expected to significantly impact the quality of the drug products. These outstanding issues will be addressed, as agreed upon with the applicant, via post-marketing commitments (PMCs) and a concurrent filing of a CBE-30. A number of PMCs relate to establishing a validated analytical method for control of a polymorphic form in the tablet drug product specification using x-ray powder diffraction (XRPD) and including a testing facility for this new method. Other PMCs are to provide results from the on-going requalification of the sterility test method and data to support in process control limits for the intravenous drug product.

Nonclinical Pharmacology/Toxicology

The Pharmacology Toxicology reviewer recommended approval of these NDAs. I concur that there are no Pharmacology Toxicology issues precluding approval.

Reproductive and developmental toxicology studies did not include the excipient sulfobutylether beta-cyclodextrin (SBECD) in the test article formulation. Since this excipient might alter the pharmacokinetics of delafloxacin, there are two post-marketing requirements (PMRs) related to evaluating delafloxacin distribution and effects in the presence of this excipient. One PMR is to conduct a tissue distribution study in pregnant rats treated during the period of organogenesis with the oral formulation and with the intravenous formulation with the excipient SBECD to assess the distribution of the drug substance to the reproductive tract and developing fetus. If the results of the tissue distribution study demonstrate greater exposure of the fetus / maternal reproductive tract to delafloxacin with the intravenous formulation, the applicant will be required to conduct an embryo-fetal developmental toxicology study in pregnant rats treated during the period of organogenesis with the

intravenous formulation to identify possible effects of delafloxacin with the excipient SBECD on fetal development during the period of organogenesis.

Clinical Pharmacology

The Clinical Pharmacology Reviewer concluded that the NDAs are approvable from a Clinical Pharmacology perspective. I concur that there are no Clinical Pharmacology issues precluding approval.

The reviewer agreed with the recommended dosage regimen of 300 mg every 12 hours (Q12h) administered by IV infusion over 60 minutes or 450 mg Q12h orally (with or without food) at the discretion of the physician for a total duration of 5 to 14 days. In patients with severe renal impairment, the reviewer agreed with the applicant's proposal to reduce the IV dose to 200 mg q12h, (b) (4)

The reviewer recommended against the use of delafloxacin in patients with end stage renal disease (ESRD) due to: concerns regarding drug disposition following oral dosing and no patient data, data limitations regarding off-dialysis day exposure in the renal impairment study, and concerns regarding accumulation of the excipient SBECD in the IV formulation that may pose a nephrotoxicity risk. These recommendations were accepted by the applicant and are included in labeling.

Clinical Microbiology

The Clinical Microbiology reviewer recommended approval pending agreement on labeling. I concur that there are no Clinical Microbiology issues precluding approval.

Susceptibility test interpretive criteria were established using MIC distribution data from surveillance studies, PK/PD analyses, and clinical data from the Phase 3 trials. These were agreed to by the applicant and are included in labeling.

Clinical/Statistical – Efficacy

The Statistical reviewer concluded that delafloxacin was noninferior to comparator in two adequate and well controlled trials and provides evidence to support the efficacy of delafloxacin for the treatment of ABSSSI. The Clinical reviewer also concluded that the applicant provided adequate evidence for the efficacy of delafloxacin in ABSSSI. The CDTL and Division Director concluded that the applicant has provided substantial evidence of effectiveness to support approval of delafloxacin for the treatment of ABSSSI in adult patients. I agree with these conclusions.

The applicant submitted two Phase 3 trials to these NDAs. Study RX-3341-302 (Study 302) was a multicenter, randomized, double-blind trial in which the efficacy and safety of IV delafloxacin was compared to that of IV vancomycin plus aztreonam in the treatment of ABSSSI. Study RX-3341-303 (Study 303) was a multicenter, randomized, double-blind trial in which the efficacy and safety of IV and oral delafloxacin was compared to that of IV

vancomycin plus aztreonam in the treatment of ABSSSI. The design of both of these trials was consistent with recommendations in FDA guidance.² The primary endpoint was objective response of $\geq 20\%$ reduction in lesion erythema compared with baseline as determined by digital measurement of the leading edge at 48 to 72 hours (± 2 hours) after initiation of therapy, with no evidence of clinical failure. The primary analysis population was the intent-to-treat (ITT) population.

Table 1 shows the objective clinical response rates at the 48 to 72 hour assessment for Studies 302 and 303. In each trial, the lower limit of the 95% confidence interval for the treatment difference was greater than -10%, demonstrating that delafloxacin was noninferior to vancomycin plus aztreonam for the treatment of ABSSSI.

Table 1: Objective Clinical Response at 48 to 72 Hours (ITT Population)

	Study 302			Study 303		
	Delafloxacin IV N=331	Vancomycin + aztreonam N=329	Treatment difference ¹ (95% CI)	Delafloxacin IV/PO N=423	Vancomycin + aztreonam N=427	Treatment difference ¹ (95% CI)
Clinical response, n (%)	259 (78.2)	266 (80.9)	-2.6 (-8.8, 3.6)	354 (83.7)	344 (80.6)	3.1 (-2.0, 8.3)

¹ Treatment difference, expressed as percentages based on Mantel Haenszel methods to account for stratification by infection site in study 302, and for stratification by BMI and infection type in Study 303

CI = confidence interval

Adapted from FDA statistical review, Table 14

At the Day 14 follow-up assessment in the ITT population, investigator assessed response results were similar to the early clinical response with no drop-off observed in any of the treatment arms.

Safety

The Clinical Reviewer, CDTL, and Division Director concluded that there were no safety issues precluding approval. I conclude that the benefit-risk is favorable under the conditions recommended in labeling.

A total of 1,682 subjects/patients were exposed to delafloxacin during clinical development, with 741 patients receiving delafloxacin in the pooled Phase 3 trials. In the pooled Phase 3 trials, there was one death in the delafloxacin arms and four in the comparator arms; all decedents had multiple co-morbidities. There were no notable imbalances in serious adverse events or treatment emergent adverse events leading to discontinuation. The most common adverse reactions leading to study discontinuation in the delafloxacin arms were urticaria (2/741) and hypersensitivity (2/741); the frequency was similar in the comparator arms. Adverse reactions occurring in $\geq 2\%$ of patients receiving delafloxacin were: nausea, diarrhea, headache, transaminase elevations, and vomiting, with nausea and diarrhea reported more frequently in delafloxacin patients than comparator. Transaminase elevations were balanced between delafloxacin and comparator and there were no Hy's Law cases. Three patients treated with delafloxacin had transaminase elevation in the Grade 3 or 4 range. In two of these

² FDA guidance for industry *Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment* (October, 2013)

patients, there was use of concomitant hepatotoxic medications. The third case was assessed by the Clinical reviewer as likely related to an HCV flare or acute HCV, and I concur with this assessment.

Advisory Committee Meeting

An Advisory Committee was not convened as there were no issues raised in the course of NDA review that would benefit from an Advisory Committee discussion.

Pediatrics

The PeRC concurred with the Division recommendation of a full waiver of pediatric studies for ABSSSI because of safety concerns (fluoroquinolones cause arthropathy in juvenile animals) and the drug does not represent a meaningful therapeutic benefit over existing therapies and would not be expected to be used in a substantial number of pediatric patients.

Labeling

As delafloxacin is a member of the fluoroquinolone class of antibacterial drugs, safety issues related to the class will be included in relevant sections of labeling including the Boxed Warning and Warning and Precautions section. A Medication Guide is also being included as part of labeling to convey important safety information to patients.

REMS

The Division of Risk Management (DRISK) reviewer concluded that a REMS is not needed to ensure the benefits of delafloxacin outweigh its risks. Labeling, including the Medication Guide, routine pharmacovigilance, and postmarketing requirements were considered adequate to address the safety issues at this time. I concur with this assessment.

Postmarketing Requirements and Commitments

These are detailed in the Division Director Review and the Approval Letter.

There are three Postmarketing Requirements including:

- Conducting U.S. surveillance studies for five years from the date of marketing to determine if resistance to delafloxacin has developed in those organisms specific to the indication in the label for ABSSSI.
- Two studies related to evaluating delafloxacin distribution and effects in the presence of the SBECD excipient described above under Pharmacology/Toxicology.

The applicant has agreed to five Postmarketing Commitments related to Chemistry Manufacturing and Controls described above under Product Quality.

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/s/

JOHN J FARLEY
06/19/2017