CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208114Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # **208114** SUPPL # HFD # **161**

Trade Name **DEFITELIO**

Generic Name **Defibrotide Sodium**

Applicant Name **Gentium S.r.L. (a Jazz Pharmaceuticals company)**

Approval Date, If Known **March xx, 2016**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7 years

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ NO ☐

Explain:

Investigation #2

IND # YES ☐ NO ☐

Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: **Beatrice Kallungal**
Title: **Senior Regulatory Project Manager**
Date: **03/30/2016**

Name of Office/Division Director signing form: **Ann T. Farrell, MD**
Title: **Division Director**

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BEATRICE A KALLUNGAL
03/30/2016

ANN T FARRELL
03/30/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # **208114** BLA # N/A	NDA Supplement # **N/A** BLA Supplement # N/A	If NDA, Efficacy Supplement Type: **N/A** *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: **DEFITELIO** Established/Proper Name: **Defibrotide** Dosage Form: **Solution**		Applicant: **Gentium S.r.L. (a Jazz Pharmaceuticals company)** Agent for Applicant (if applicable): **N/A**
RPM: **Beatrice Kallungal**		Division: **Division of Hematology Products**

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is **March 31, 2016**	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): **NME (Under the program)**
(confirm chemical classification at time of approval)

☒ Fast Track
☒ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other ASCO Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	**Approval; 3/30/2016**
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	**Conditionally Acceptable** **9/15/2015** **9/14/2015**
❖ Labeling reviews *(indicate dates of reviews)*	RPM: **3/9/2016** DMEPA: **12/14/2015; 11/30/2015 and 10/28/2015** DMPP/PLT (DRISK): ☒ None OPDP: **3/15/2016** SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	**3/3/2016** ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP
  ○ If yes, Center Director's Exception for Review memo *(indicate date)*
  ○ If yes, OC clearance for approval *(indicate date of clearance communication)*
	☐ Yes ☒ No
	☐ Not an AP action

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC N/A If PeRC review not necessary, explain: **Orphan drug designation**	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	**3/4/2016; 3/3/2016; 3/2/2015, 2/19/2016; 2/18/2016; 2/17/2016; 2/12/2016; 1/19/2016; 1/15/2016; 1/14/2016; 1/12/2016; 1/6/2016; 12/30/2015; 12/21/2015; 12/1/2015; 11/23/2015; 11/18/2015; 11/13/2015; 11/5/2015; 11/2/2015 (2); 10/26/2015; 10/23/2015; 10/22/2015; 10/20/2015; 10/5/2015; 10/01/2015; 9/29/2015; 9/17/2015; 8/07/2015; 8/4/2015; 7/21/2015**
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	**8/21/2014**
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	**11/23/2015**
• Late-cycle Meeting *(indicate date of mtg)*	**1/29/2016**
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	**8/7/2014**

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	**3/30/2016**
Division Director Summary Review *(indicate date for each review)*	**3/29/2016**
Cross-Discipline Team Leader Review *(indicate date for each review)*	**3/3/2016**
PMR/PMC Development Templates *(indicate total number)*	**3**
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	**2/17/2016**
• Clinical review(s) *(indicate date for each review)*	**2/11/2016**;
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	**See page 197 of clinical review dated 2/11/2016**
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	**3/18/2016 Consult for Rare Pediatric Disease Determination**
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	 **N/A** **N/A** **12/29/2015**
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	**2/16/2016**
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	**Cosigned addendum review dated 3/11/2016 and primary review dated 1/11/2016**
Statistical Team Leader Review(s) *(indicate date for each review)*	**Cosigned addendum review dated 3/11/2016 and primary review dated 1/11/2016**
Statistical Review(s) *(indicate date for each review)*	**3/11/2016 addendum review 1/11/2016 primary review**

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	**Cosigned primary review dated 12/24/2015**
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	**Cosigned primary review dated 12/24/2015**
Clinical Pharmacology review(s) *(indicate date for each review)*	**2/8/2016 QT study review 12/24/2015 primary review**
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	**1/12/2016**
• Supervisory Review(s) *(indicate date for each review)*	**1/4/2016**
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**12/30/2015**
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	**12/31/2015**
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	**12/17/2015 microbiology review**
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	**See page 97 of product quality review dated 12/31/2015**
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BEATRICE A KALLUNGAL
03/30/2016

From: Patel, Soumya
Sent: Thursday, March 03, 2016 1:43 PM
To: robin.hume@jazzpharma.com
Subject: Rare Pediatric Disease Voucher Request for Hepatic Veno-Occlusive Disease following HSCT - Follow-up Questions
Importance: High

Dear Robin,

Additional information which affects the proportions of pediatric and adult patients with hepatic VOD has come to our attention and we'd like to obtain your input/feedback regarding this additional material.

1. The data from the CIBMTR database (see http://bloodcell.transplant.hrsa.gov/research/transplant_data/transplant_activity_report/year-age_group.pdf) notes that in 2013 there were 19,220 transplants. Of these 19,220 transplants, 2408 occurred in 0-20 year olds and the remaining 16,812 occurred in >20 year olds.

   The 13.7% mean incidence noted in the Coppell paper that you note is a general mean incidence for hepatic VOD in hsct patients. Taking 13.7% of 19,220 results in 2,633 patients in 2013 who had hepatic VOD post hsct. A paper by Corbacioglu et al (see Expert Rev Hematol 2012; 5[5]:291-302) notes that the mean incidence of hepatic VOD in children is 25%. Applying this to the 2,408 hsct transplants conducted in children results in 602 cases of children with post hsct hepatic vod. This would leave 2031 adults with post hsct hepatic vod (2633-602) and demonstrates that >50% of the hepatic vod population are adults.

   If you are in disagreement with the above data, please elaborate as to why you disagree.

2. You have furnished in Appendix 2 in your follow-up email response to our questions, the following table:

Appendix 2 Characteristics of Patients Who Underwent Transplantation in the United States Reported to the CIBMTR with VOD from 2008-2014

Variable	Non-severe VOD	Severe VOD
Number of patients	**343**	**320**
Number of centers	94	94
Age at transplant, years		
Median (range)	24 (<1-72)	19 (<1-73)
≤18	156 (45)	148 (46)
19-59	153 (45)	134 (42)
60-64	15 (4)	23 (7)
≥65	19 (5)	15 (5)
Type of transplant		
Autologous	15 (4)	18 (6)
Allogeneic	328 (94)	302 (94)
Year of transplant		
2008	88 (24)	85 (27)
2009	70 (21)	71 (22)
2010	49 (15)	47 (15)
2011	26 (8)	23 (7)
2012	30 (9)	31 (10)
2013	43 (12)	34 (11)
2014	37 (11)	29 (9)

Patients with no VOD during this time period: 18,683
All patients undergoing transplantation by age during this time period:
≤18: 3316 (17%)
19-59: 10182 (53%)
60-64: 2595 (13%)
≥65: 3253 (17%)

Definition of VOD: Physician assessment of 'yes' corresponding to Question 464 on Form 2100 "Did the recipient develop non-infectious liver toxicity (excluding GVHD) after the start of the preparative regimen to the date of last contact?" as well as a 'yes' to Question 467, which specifies the etiology as "veno-occlusive disease/sinusoidal obstruction syndrome."

Definition of severe VOD: Patient has VOD as described above and has **either** i) Physician response 'yes' to Question 511 "renal failure severe enough to warrant dialysis ***OR*** ii) Physician response 'yes' to Question 433 on Form 2100 "Did the recipient develop non-infectious pulmonary abnormalities (other than interstitial pneumonitis/idiopathic pneumonia syndrome/adult respiratory distress syndrome) after the date of last contact?"

Can you provide the breakdown for the number of patients with VOD for 2014 (n=66) who were <19 years of age and ≥19 years of age? It is not clear how you have actually obtained this data. Please provide references in your response for this table and any figures derived using this table.

Thank you.

Soumya Patel Pharm.D.
FDA/OOPD

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/s/

BEATRICE A KALLUNGAL
03/15/2016

From:	Kallungal, Beatrice
To:	Robin Hume (Robin.Hume@jazzpharma.com)
Cc:	Kallungal, Beatrice
Subject:	NDA 208114, Defibrotide - Draft Package Insert with FDA"s Revisions dated 03/04/2016
Date:	Friday, March 04, 2016 5:27:02 PM
Attachments:	NDA 208114 Defibrotide draft-labeling-03042016.docx

Dear Robin,
Attached is the draft package insert (PI) for NDA 208114, Defibrotide with FDA's revisions.

Please review the FDA's changes/comments and using the same draft, do the following:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition, please review the document for formatting. See *PLR Requirements for Prescribing Information internet site*

We request that you respond by **Noon EST, Tuesday March 8, 2016** via e-mail and officially submit to the NDA.

If you have any questions, feel free to contact me.

Kind regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
03/04/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208114

INFORMATION REQUEST

Gentium S.p.A (Jazz Pharmaceuticals, Inc.)
Attention: Robin L. Hume
Director of Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Hume:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for defibrotide.

We also refer to your July 31, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

(b) (4)

If you have any questions, please contact me, at (240) 402-6153. Please respond by March 4, 2016.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Laiq -A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -A, 0.9.2342.19200300.100.1.1=2001555007
Date: 2016.03.02 14:39:58 -05'00'

From: Kallungal, Beatrice
To: Robin Hume; Amanda Roodhouse (Amanda.Roodhouse@jazzpharma.com)
Cc: Kallungal, Beatrice
Subject: RE: NDA 208114, Defibrotide PMC - Information request 02/18/2016
Date: Thursday, February 18, 2016 1:58:18 PM

Hi Robin and Amanda,
The team has reviewed the submissions with the Applicant-proposed revisions to PMC1 and PMC2, received on 1/6/2016 and 2/16/2016. Please find below, the Division's suggestions:

> *The FDA has evaluated you proposed modification to PMC 1 and PMC2 and the proposed changes are not acceptable* (b) (4)
>
> (b) (4)
>
> *Useful guidance may be found in sources such as: CDER Draft Guidance for Industry Immunogenicity Assessment for Therapeutic Protein Products (FDA Draft Guidance, 2013) and CDER Draft Guidance for Industry: Assay development for immunogenicity testing of therapeutic proteins (FDA Draft Guidance, 2009).*

Please officially submit the revised PMCs to the NDA (and e-mail a courtesy copy to me) by **10 am EST Monday February 22, 2016.**

Regards,

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

From: Robin Hume [mailto:Robin.Hume@jazzpharma.com]
Sent: Wednesday, February 17, 2016 11:48 AM
To: Kallungal, Beatrice
Cc: Robin Hume
Subject: RE: NDA 208114, Defibrotide PMC #2

Hi Beatrice,

Thanks for the follow up. Please note that the submission we made yesterday is the most comprehensive information and inclusive of PMC1 and PMC2 responses. Can you please confirm that the review team has both the original (1/6/2016) PMC1 and PMC2 response as well as the response from 2/16/2016?

Thank you
Robin

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/s/

BEATRICE A KALLUNGAL
02/19/2016

From:	Kallungal, Beatrice
To:	Robin Hume (Robin.Hume@jazzpharma.com); Amanda Roodhouse (Amanda.Roodhouse@jazzpharma.com)
Cc:	Kallungal, Beatrice
Subject:	NDA 208114, Defibrotide - Draft Package Insert with FDA"s Revisions dated 02/19/2016
Date:	Friday, February 19, 2016 2:45:57 PM
Attachments:	NDA 208114 Defibrotide draft-labeling-02192016.docx

Dear Robin and Amanda,
Attached is the draft package insert (PI) for NDA 208114, Defibrotide with FDA's revisions.

Please review the FDA's changes/comments and using the same draft, do the following:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

We request that you respond by **3 pm EST, Wednesday February 24, 2016** via e-mail and officially submit to the NDA.

Please note, if your team would like to discuss the proposed revisions with the Agency, I have blocked the calendars for a half our teleconference on **Tuesday February 23, 2016 at 1:30 pm EST**. Clinical and statistical review team members are invited to this meeting. If you wish to have any other disciplines to be in attendance, please let me know. Also please let me know whether you wish to take advantage of this teleconference.

If you have any questions, feel free to contact me.

Kind regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

BEATRICE A KALLUNGAL
02/19/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208114

INFORMATION REQUEST

Gentium S.p.A (Jazz Pharmaceuticals, Inc.)
Attention: Robin L. Hume
Director of Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Hume:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for defibrotide.

We also refer to your July 31, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

The Biological Assay (b) (4) methods were evaluated and are not acceptable for quality control or regulatory purposes. Please address the following issues and submit the revised method.

(b) (4)

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

(b) (4)

(b) (4)

If you have any questions, please contact me, at (240) 402-6153. Please respond by February 24, 2016.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Laiq -A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -A, 0.9.2342.19200300.100.1.1=2001555007
Date: 2016.02.17 11:36:44 -05'00'

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208114

INFORMATION REQUEST

Gentium S.p.A (Jazz Pharmaceuticals, Inc.)
Attention: Robin L. Hume
Director of Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Hume:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for defibrotide.

We also refer to your July 31, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. **Correct the compendial status for both hydrochloride acid and sodium hydroxide in the carton label. They both should be NF,** (b) (4)

If you have any questions, please contact me, at (240) 402-6153. Please respond by February 17, 2016.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Laiq -A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -A, 0.9.2342.19200300.100.1.1=2001555007
Date: 2016.02.12 14:01:49 -05'00'

From:	Kallungal, Beatrice
To:	Robin Hume (Robin.Hume@jazzpharma.com)
Cc:	Kallungal, Beatrice
Subject:	NDA 208114, Defibrotide - Informaiton request
Date:	Tuesday, January 19, 2016 6:38:34 PM

Hi Robin,
Please refer to NDA 208114, Defibrotide. Please provide your response via e-mail by **Noon EST Thursday January 21, 2016** and officially submit to the NDA

The eg.xpt only has safety ECGs, please submit the Holter ECGs in SDTM format, including the primary endpoint QTcI and its correction factor, etc. In addition, please submit ECG waveform files with annotations for this study to the ECG warehouse at: www.ecgwarehouse.com .

Please acknowledge the receipt of this request.

Thanks,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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BEATRICE A KALLUNGAL
01/19/2016

From:	Kallungal, Beatrice
To:	Robin Hume (Robin.Hume@jazzpharma.com); Amanda Roodhouse (Amanda.Roodhouse@jazzpharma.com)
Cc:	Kallungal, Beatrice
Subject:	NDA 208114, Defibrotide - Draft Package Insert with FDA"s Revisions dated 01/15/2016
Date:	Friday, January 15, 2016 3:48:02 PM
Attachments:	NDA 208114-draft-uspi 01152016.docx

Dear Robin and Amanda,
Attached is the draft package insert (PI) with FDA's revisions for NDA 208114, Defibrotide.

Please review the FDA's changes/comments and using the same draft, do the following:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

We request that you respond by **11 am EST, Friday January 22, 2016** via e-mail and officially submit to the NDA.

If you have any questions, feel free to contact me.

Kind regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
01/15/2016

From:	Kallungal, Beatrice
To:	Robin Hume (Robin.Hume@jazzpharma.com)
Cc:	Kallungal, Beatrice
Subject:	NDA 208114, Defibrotide - Informaiton request
Date:	Thursday, January 14, 2016 6:12:50 PM
Attachments:	Highlights_ClinPharm_and_Cardiac_Safety.doc

Hi Robin,
Please refer to NDA 208114, Defibrotide. Please provide your response via e-mail by **Noon EST Tuesday January 19, 2016** and officially submit to the NDA

As we review the final results of the QT study report R09-1425, entitled **"***A Double-Blind Randomized Crossover Trial to Define the ECG Effects of Defibrotide Using a Clinical and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women: a Thorough ECG Trial*", please complete the enclosed ClinPharm and Cardiac Safety Table and send it back.

Please acknowledge the receipt of this request.

Thanks,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

Table 1. Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose and exposure	Include maximum proposed clinical dosing regimen Mean (%CV) Cmax and AUC at the single maximum proposed clinical dose Mean (%CV) Cmax and AUC at the steady state with the maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	• Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t½	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	
Preclinical Cardiac Safety	Summarize *in vitro* and *in vivo* results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

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/s/

BEATRICE A KALLUNGAL
01/15/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208114

INFORMATION REQUEST

Gentium S.p.A (Jazz Pharmaceuticals, Inc.)
Attention: Robin L. Hume
Director of Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Hume:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for defibrotide.

We also refer to your July 31, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

For both vial and container labels:

1. (b) (4)

For vial label:

1. Add the statement of "Rx only" as per 21 CFR 201.100(b)(1)
2. Change (b) (4) to single-patient-use vial

For container label:

1. Add the statement of "sterile"
2. Add compendial status and quantitative information for each ingredient for injectable product as per 21 CFR 201.100(b)(5)(iii)
3. Change (b) (4) to single-patient-use vial
4. Storage should read as "store at 20oC to 25oC (68oF to 77oF), excursions permitted between 15oC and 30oC (between 59oF and 86oF).

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by COB January 15, 2016.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Rabiya Laiq -A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -A, 0.9.2342.19200300.100.1.1=2001555007
Date: 2016.01.12 13:11:12 -05'00'

From:	Kallungal, Beatrice
To:	Robin Hume (Robin.Hume@jazzpharma.com)
Cc:	Kallungal, Beatrice
Subject:	NDA 208114, Defibrotide PMR studies
Date:	Wednesday, January 06, 2016 2:32:07 PM
Importance:	High

Dear Robin,

Please refer to NDA 208114, Defibrotide. Please provide your response by **Noon EST Monday January 11, 2016**.

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by telecon, if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that has already received full concurrence by FDA.

PMR #1 Description: Conduct an analysis of safety in a randomized, open-label multi-center clinical trial comparing defibrotide versus best supportive care in the prevention of hepatic VOD in adult and pediatric patients, including all adverse events, laboratory abnormalities and frequent peri-infusion vital signs.

PMR Schedule Milestones:

Final Protocol Submission:

MM//YYYY

Study Completion: MM//YYYY

Final Report Submission: MM//YYYY

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR or PMC designation numbers will be assigned later

Some things you can do to expedite this process:

1. For labeling and PMRs or PMCs reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially

submit. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs or PMCs as agreed upon. We ask the following:

a. For any new study to address a PMR /PMC, it is necessary to submit the protocol for DHP review and concurrence prior to initiating the study. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.

b. Send the RPM an email courtesy copy of the draft versions of the protocol, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.

c. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR or PMC NUMBER). This helps the document room and DHP to code the submission properly. All protocol submissions are made to the IND.

Regards,

Beatrice

Beatrice Kallungal

Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)

FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)

(301) 796-9845 (fax)

E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
01/06/2016

Leaman, Diane V

From:	Leaman, Diane V
Sent:	Wednesday, December 30, 2015 11:47 AM
To:	'robin.hume@jazzpharma.com'
Cc:	Kallungal, Beatrice
Subject:	Defibrotide PMC studies
Importance:	High

Tracking:	**Recipient**	**Delivery**
	'robin.hume@jazzpharma.com'	
	Kallungal, Beatrice	Delivered: 12/30/2015 11:47 AM

Dear Robin,

I am sending this for Beatrice Kallungal who is currently out of the office.

Please refer to NDA 208114, Defibrotide. Please provide your response by **Noon EST Wednesday January 6, 2016.**
As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by telecon, if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that has already received full concurrence by FDA.

PMC #1 Description: Develop sensitive and specific anti-drug (defibrotide) binding and neutralizing assays. Submit validation reports on the assays in a final report to the NDA.

PMC Schedule Milestone: Final Report Submission MM/YYYY

PMC #2 Description: Evaluate patients' sera for binding and neutralizing antibodies to defibrotide using the validated assays from PMC 1 and submit the data in a final immunogenicity study report.

PMC Schedule Milestones:

Final Protocol Submission:	MM//YYYY
Study Completion:	MM//YYYY
Final Report Submission:	MM//YYYY

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR and PMC studies/trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR or PMC designation numbers will be assigned later

Please note that the Division is in the process of drafting a safety PMR which we will send in the next two weeks.

Some things you can do to expedite this process:

1. For labeling and PMRs or PMCs reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs or PMCs as agreed upon. We ask the following:
   a. For any new study to address a PMR /PMC, it is necessary to submit the protocol for DHP review and concurrence prior to initiating the study. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol and DHP has advised you that the protocol is judged acceptable to address the PMR/PMC. A fulfillment decision requires review.
   b. Send the RPM an email courtesy copy of the draft versions of the protocol, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.
   c. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR or PMC NUMBER). This helps the document room and DHP to code the submission properly. <u>All protocol submissions are made to the IND.</u>

Diane Leaman
Safety Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
(301) 796-1424

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/s/

DIANE V LEAMAN
12/31/2015

From:	Kallungal, Beatrice
To:	Robin Hume (Robin.Hume@jazzpharma.com)
Cc:	Kallungal, Beatrice
Subject:	NDA 208114, Defibrotide - Draft Package Insert with FDA"s Revisions
Date:	Monday, December 21, 2015 12:59:44 PM
Attachments:	NDA 208114_draft-USPI-12212015.docx

Dear Robin,
Attached is the draft package insert (PI) with FDA's revisions for NDA 208114, Defibrotide.

Please review the FDA's changes/comments and using the same draft, do the following:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you do not agree with the labeling revisions, provide your comments and proposed language (shown in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

We request that you respond by **Noon EST, Monday December 28, 2015** via e-mail and officially submit to the NDA.

If you have any questions, feel free to contact me.

Kind regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

BEATRICE A KALLUNGAL
12/21/2015

From:	Kallungal, Beatrice
To:	Robin Hume
Cc:	Kallungal, Beatrice
Subject:	NDA 208114, Defibrotide - Labeling Information request 12/1/2015
Date:	Tuesday, December 01, 2015 3:57:59 PM

Hi Robin,
Please find below additional information request for NDA 208114 labeling. Please submit your response to this request via e-mail by **4 pm EST Monday December 7, 2015** followed by officially submitting the response to the NDA.

A. *Container label*
   1. *Revise the statement* (b) (4) *to read "For intravenous infusion only" as solution for intravenous injection is not an acceptable dosage form.*

B. *Carton labeling*
   1. *See A.1 and revise the carton labeling accordingly.*
   2. *To minimize the risk of the product being administered without dilution, we recommend moving the warning statement "Must be diluted before intravenous infusion" to the principal display panel if space permits.*

Please acknowledge the receipt of this request.

Regards,

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
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/s/

BEATRICE A KALLUNGAL
12/01/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208114

MID-CYCLE COMMUNICATION

Gentium S.p.A.
c/o Jazz Pharmaceuticals, Inc.
Attention: Robin Hume, MS, RAC
Director, Regulatory Affairs, US Agent
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Hume:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Defibrotide solution for infusion, 200 mg/2.5mL.

We also refer to the teleconference between representatives of your firm and the FDA on November 23, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: November 23, 2015

Application Number: NDA 208114

Product Name: Defibrotide
Indication: For the treatment of hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with (b) (4) dysfunction following hematopoietic stem-cell transplantation (HSCT).

Applicant Name: Gentium S.p.A. (a Jazz Pharmaceuticals company)

Meeting Chair: R. Angelo de Claro, MD
Meeting Recorder: Beatrice Kallungal, BS

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Ann Farrell, MD, Director
R. Angelo de Claro, MD, Clinical Team Leader
Donna Przepiorka, MD, PhD, Clinical Reviewer
Tanya Wroblewski, MD, Clinical Reviewer
Theresa Carioti, MPH, Chief Project Management Staff
Beatrice Kallungal, BS, Senior Regulatory Project Manager

Office of Biostatistics/Division of Biometrics V
Yuan-Li Shen, PhD, Team Leader

OHOP/Division of Hematology, Oncology, Toxicology
Christopher Sheth, PhD, Supervisory Pharmacologist

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Bahru Habtemariam, PharmD, Acting Team Leader
Guoxiang (George) Shen, Reviewer

Office of Pharmaceutical Quality (OPQ)/Division of New Drug Products
Olen Stephen, PhD, Branch Chief

OPQ/Office of Process and Facilities (OPF)/Division of Inspectional Assessment (DIA)
Quallyna Porte, Interdisciplinary Scientist

Office of Surveillance and Epidemiology (OSE), Division of Epidemiology I (DEPI I)
Carolyn McCloskey, MD, MPH, Epidemiologist
Sarah Harris, PharmD, Safety Regulatory Project Manager

Office of Medication Error Prevention & Risk Management (OMEPRM)/Division of Risk Management (DRISK)
Naomi Redd, PharmD, Acting Team Leader

EASTERN RESEARCH GROUP ATTENDEES
Chris Sese, independent Assessor

APPLICANT ATTENDEES
Joanne Curley, Executive Director, Global Promotional Regulatory Affairs
Charles LaPree, Head of Global Regulatory Affairs
Juli Miller, Associate Director, Medical Writing
Patty Moore, Vice President, Quality R&D
Krishna Allamneni, Executive Director, Nonclinical and Early Development
Jennifer Ekelund, Vice President, US Regulatory Affairs
Mark Eller, Head of Early Development and Clinical Pharmacology
Robin Hume, Director, Regulatory Affairs, Jazz/US Agent for Gentium
Chinglin Lai, Vice President, Biostatistics
Maja Miloslavsky, Senior Director, Biostatistics
Amanda Roodhouse, Manager, Regulatory Strategy
Christy Wood, Senior Manager, Regulatory Affairs
Jin Zhu, Director, Biostatistics
Katie Zomordi, Senior Director, Early Development
Bill Bennett, Head of Biologics Development
Eileen Connolly, Associate Director, Global Regulatory Affairs, CMC
Tim Corn, Development Team Leader Hematology/Oncology
Catherine Lunny, Head of Global Regulatory Affairs, CMC
John Miller, Global Product Team Lead
Joel Selcher, Executive Director, Global Regulatory Affairs
(b) (4)

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we

may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

We request that you provide an item-by-item response for each item in Sections 2.0 and 3.0 by December 9, 2015.

2.0 SIGNIFICANT ISSUES

Clinical

1. The instructions for adverse event recording in the pivotal trial and the supporting studies excepted many events. As such, the safety profile for defibrotide (b) (4) may be incomplete. In order to confirm the verity of the proposed safety profile, you will need to submit safety results from a trial of defibrotide which required reporting of all adverse events.

2. The assessment of vital signs in the pivotal trial and the supporting studies was limited to daily measurement. This is not sufficient to objectively exclude the occurrence of infusion reactions. You will need to submit frequent measurements of vital signs during and immediately after infusion of defibrotide in a clinical study in order to assess objectively the incidence of infusion reactions.

3. You have provided no measurements of anti-drug antibodies in subjects treated with defibrotide. The need for such an evaluation is still under review.

Statistics

1. The statistical significance level cannot be determined due to many unplanned adaptations, e.g. sample size reduction and planned/unplanned interim analyses.

2. Adjusted comparative results based on day 100 survival rate varied by which propensity score defined strata was used. Whether or not the propensity score adjusted analysis have sufficiently balanced the between treatment difference cannot be determined. Also, the property of the analysis method is not known when sample size is small and distribution of the strata level is sparse. Therefore, the proposed efficacy claims based on an analysis stratified by quintile of propensity scores is questionable.

Product Quality

1. The manufacturing process is unclear with regards to the expression of strength of the drug substance, (b) (4) The calculation of assay also does not clarify the expression of the drug substance (b) (4)

(b) (4)

(b) (4)

2. Provide data to demonstrate the compatibility of filters with the drug product. Also, please indicate whether (b) (4) is used in the manufacturing process of the product. If (b) (4) is used, specify the type (b) (4) Provide justification or study to support the material selection.

3.0 INFORMATION REQUESTS

Clinical

1. In response to Question #3 in the information request sent 11/2/2015, you indicated that you do not currently have access to the clinical study reports and data for the marketing application in Italy. Please clarify which randomized studies for non-VOD indications listed in Appendix 1 of your response or in the Investigator's Brochure were conducted by you or your predecessors in the development of defibrotide, and clarify when you will have access to the clinical study reports and data for these studies.

2. The clinical study report for Protocol 2004-000592-33 indicates that 24 subjects in the defibrotide arm developed VOD and 39 in the control arm developed VOD (Figure 2). Please identify which flags in the data files identify subjects who developed VOD at any time vs VOD by Day +30. Please also identify the variable with date of onset of VOD occurring at any time.

3. You also provide a flag in the data files for Protocol 2004-000592-33 for multiorgan failure by day +100. Please clarify if that flag is for multiorgan failure in any subject on study or only for subjects who developed VOD by Day +30. If the latter, please clarify if there is a flag for subjects who developed multiorgan failure independent of whether there was VOD.

4. We remind you of the outstanding Information Request sent 11/13/2015: Please obtain and submit the financial disclosure information for the phase 2 dose-finding study 99-118.

Statistics

Provide the 95% CIs for the day 100 survival rate and complete response rate estimates by treatment arm using the exact method for study 2005-01.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At this time, there are no major safety concerns identified and currently, there is no need for a Risk Evaluation and Mitigation Strategy (REMS).

Refer to Section 2.0 regarding significant issues regarding safety data.

5.0 ADVISORY COMMITTEE MEETING

At this time, there are no plans for an Advisory Committee meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The late-cycle meeting is scheduled for January 26, 2016 at 10:00 AM EST. We plan to communicate proposed labeling and, if necessary, any post-marketing requirement/commitment requests by January 2, 2016. As communicated earlier, the user fee goal date for NDA 208114 is March 31, 2016.

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/s/

ROMEO A DE CLARO
11/24/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208114

INFORMATION REQUEST

Gentium S.p.A (Jazz Pharmaceuticals, Inc.)
Attention: Robin L. Hume
Director of Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Hume:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for defibrotide.

We also refer to your July 31, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The proposed storage time after dilution into 5% Dextrose injection or 0.9% sodium chloride injection is 24 hours but the storage temperature was not provided in the label. The Agency recommends that storage times greater than 4 hours at room temperature or 24 hours under refrigeration be supported with microbiological data that demonstrates adventitious microbial contamination does not grow under the storage conditions. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E (http://www.fda.gov/downloads/Drugs/Guidances/ucm073507.pdf) and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7 (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073369.pdf) .

   If studies are conducted, the report should describe test methods and results that employ a minimum countable inoculum to simulate potential microbial contamination that may occur during product dilution. It is generally accepted that growth is evident when the population increases more than 0.5 Log_{10}. The test should be run at the label's recommended storage conditions and be conducted for 2 to 3-times the label's

recommended storage period and using the label-recommended fluids. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-constitution storage period is not more than 4 hours at room temperature or 24 hours refrigeration.

2. Using the data provided in Table 6, FDA generated a plot that differs from Figure 4. Elaborate how the data presented in Table 6 of Section 3.2.P.2.2 support your conclusion that the drug product solutions with pH (b) (4) are more stable (b) (4)

Table 6. Analytical Results of Defibrotide Solutions of Different pH Stored at (b) (4) RH for 12 Weeks

(b) (4)

Figure 4. Bivariate Fit of Slope Free Nucleic Acid/Time by pH

(b) (4)

3. We have noted that different acceptance criterion for osmolarity have been used in different sections of 3.2.P.5. For example, osmolarity is listed as (b) (4) mOsm/L in the 3.2.P.5.1 Specification which is different from the one listed in the 3.2.P.5.6 Justification of Specification (b) (4) mOsm/L). Please clarify the proposed acceptance criterion for osmolarity and update the sections of the NDA accordingly.

4. You have proposed the acceptance criterion for polydispersity index to be ≤ (b) (4) for both drug substance and drug product. However, based on the historical data from 44 drug product batches, the value for the mean ± 3SD is (b) (4) Revise the acceptance

criterion for polydispersity to be consistent with the limit of mean ± 3SD or provide justification for lack of the (b) (4) of this attribute.

5. We have noted that elemental impurities are not controlled in the proposed drug product specification. Provide batch data to demonstrate that elemental impurity levels for the registration batches do not exceed corresponding PDE levels as per ICH Q3D or USP <232>. Also, include an adequate risk assessment that demonstrates an understanding of where elemental impurities may leach into the drug product. The risk assessment should demonstrate an understanding of these risk factors for both the current manufacturing process and potential changes to the process that may increase the risk of elemental impurity levels. Alternatively, include testing and control for elemental impurities in your proposed drug product specification.

6. The potency method validation report for (b) (4) indicates that a parallelism control is performed and potency is reported as a percentage of the reference standard. The potency method validation and batch analysis section of the NDA are deficient. Amend the NDA to contain the following:

    1) Provide a list of all lots of product and reference standard that were analyzed with the potency methods.

    2) Provide the lot number(s) of the product and reference standard that were used to validate the potency assays.

    3) Indicate the statistical program used for parallelism analysis.

    4) Provide the results for all parallelism parameters for all lots analyzed and for the lots that were used to validate the two potency methods (b) (4)

    5) Provide representative dose response graphic presentations for the parallelism analysis and indicate the test sample and reference standard for the two methods.

If you have any questions, please contact me, at (240) 402-6153. Please respond by December 1, 2015.

Sincerely,

Rabiya Laiq -A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -A, 0.9.2342.19200300.100.1.1=2001555007
Date: 2015.11.23 12:58:26 -05'00'

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

From:	Kallungal, Beatrice
To:	"Robin Hume"
Cc:	Kallungal, Beatrice
Subject:	NDA 208114, Defibrotide - Information request 11/18/2015
Date:	Wednesday, November 18, 2015 3:11:51 PM

Hi Robin,
Please find below the information request for NDA 208114. Please submit your response to this request via e-mail by **3 pm EST Monday November 20, 2015** followed by officially submitting the response to the NDA.

To assess the defibrotide effects on fibrinolytic activity, please provide the follow raw datasets:

a) *Study RQCVL050R011: datasets for plot 4.6.1 "Sigmoid dose-response curve of the Biological Plasmin Assay" and plot 4.6.3 "Evaluation of the linearity of the linear Slop-Factor of the Assay"*
b) *Study RQCVL049R011: datasets for plot 4.6.1 "Asymptotic-response curve of the Biological Assay" and plot 4.6.2 "Sigmoid dose-response curve of the Biological Assay"*
c) *Clinical study 99-118: datasets for Figure 2A: "Mean (SD) PAI-1 by Treatment Arm and Outcome".*

Please provide these datasets either as excel or sas transport files. The files should be formatted in order to quickly produce figures and plots.

Please acknowledge the receipt of this request.

Regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
11/18/2015

From:	Kallungal, Beatrice
To:	Robin Hume
Cc:	Kallungal, Beatrice
Subject:	NDA 208114, Defibrotide - Information Request - 11/13/2015
Date:	Friday, November 13, 2015 12:04:32 PM

Hi Robin,
Please find below the information request for NDA 208114. Please submit your response to this request via e-mail by **4 pm EST Monday November 30, 2015** followed by officially submitting the response to the NDA.

> *Please obtain and submit the financial disclosure information for the phase 2 dose finding study 99-118.*

Please acknowledge the receipt of this request.

Regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
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E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
11/16/2015

From:	Kallungal, Beatrice
To:	"Robin Hume"
Cc:	Kallungal, Beatrice
Subject:	NDA 208114, Defibrotide - Information request 11/05/2015
Date:	Thursday, November 05, 2015 9:04:35 AM

Hi Robin,
Please find below the information request for NDA 208114. Please submit your response to this request via e-mail by **Noon EST Friday November 06, 2015,** followed by officially submitting the response to the NDA.

- *The statistical reviewer cannot locate the SAS program that was used to compute the results in Table 27 (see CSR for study 2005-01). Please clarify where is the program located. If it is not submitted, please submit SAS codes that illustrate how the results are generated.*

Please acknowledge the receipt of this request.

Thanks,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
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/s/

BEATRICE A KALLUNGAL
11/05/2015

From: Kallungal, Beatrice
To: "Robin Hume"
Cc: Kallungal, Beatrice
Subject: NDA 208114, Defibrotide - Labeling Information request 11/02/2015
Date: Monday, November 02, 2015 2:06:07 PM

Hi Robin,
Please find below the information request for NDA 208114. Please submit your response to this request via e-mail by **4 pm EST Monday November 16, 2015** followed by officially submitting the response to the NDA.

A. *Container label*

1. *The established name is not commensurate to the prominence of the proprietary name as per CFR 201.10(g) (2). Revise the presentation of the proprietary name to use title case (i.e. Defitelio) and ensure that the established name is at least ½ the size of the proprietary name and commensurate in prominence to the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).*
2. *Revise the presentation of the established name to include the finished dosage form per USP General Chapter <1> injections. For example: Defitelio* (b) (4)
3. *Provide adequate s erical dose and the unit of measure for increased readability.*
4. (b) (4)

B. *Carton labeling*

1. *See A.1 through A.4 and revise the carton labeling accordingly.*
2. *Revise the quantity statement from* (b) (4) *to read* (b) (4)
3. *Decrease the font of the "Rx only" statement and consider placing on the side panel, as currently this statement is more prominent than other important information on the PDP.*
4. *Add the warning statement "Must be diluted before intravenous infusion" to minimize the risk of the product being administered with dilution.*
5. *The lot number and expiration date appear to be omitted from the carton labeling. We recommend adding the lot number and expiration date to ensure this critical information is available and to minimize the risk of the patient taking expired medications.*

Please acknowledge the receipt of this request.

Regards,

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
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E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
11/02/2015

From:	Kallungal, Beatrice
To:	"Robin Hume"
Cc:	Kallungal, Beatrice
Subject:	NDA 208114, Defibrotide - Information request 11/02/2015
Date:	Monday, November 02, 2015 12:39:52 PM

Hi Robin,
Please find below the information request for NDA 208114. Please submit your response to this request via e-mail by **Noon EST Friday November 06, 2015,** followed by officially submitting the response to the NDA.

1. Determining the effect of defibrotide on PAI-1 levels is a stated secondary endpoint of Protocol 99-118. Please identify where in the NDA is the data file with PAI-1 levels for this protocol.

2. Protocol 2005-01 Section 9.2.1 indicates that adverse events listed in the protocol as symptoms of the original or targeted disease are not to be considered adverse events in this study unless the event is considered serious, including adverse events that are not diagnostic of the original or targeted disease. We conclude from this text that the recording of adverse events for Protocol 2005-01 was not complete, and as such the results may not reflect the true safety profile of defibrotide. Moreover, whether the event is "considered serious" was a judgment of the investigator and may have contributed to biased reporting. Clarify how the incompleteness of adverse event recording might alter your conclusions about the safety of defibrotide in the intended patient population.

3. Provide a summary tabulation of all randomized trials of defibrotide conducted for any indication other than VOD/SOS. Include in that tabulation the dose, route, and schedule used for defibrotide administration. Please also clarify if all adverse events or only a subset of adverse events were recorded for each of these trials.

4. Submit to the NDA the legacy clinical study reports for any randomized trial of defibrotide conducted for any indication other than VOD/SOS in which adverse events were recorded without exceptions.

Please acknowledge the receipt of this request.

Thanks,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue

Silver Spring, MD 20993
(301) 796-9304 (phone)
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E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
11/02/2015

From:	Higgins, Janet
To:	"robin.hume@jazzpharma.com"
Cc:	Kallungal, Beatrice; Higgins, Janet
Subject:	NDA 208114: Defibrotide -- Information Request; Please respond by 10/30/2015
Date:	Monday, October 26, 2015 3:00:17 PM

Dear Robin Hume,

Please refer to your supplemental New Drug Application (NDA) dated July 30, 2015, received July 31, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Defibrotide Solution for infusion, 200 mg/2.5mL.

We are reviewing your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

Please clarify whether you have evaluated the immunogenicity of defibrotide in humans. If you have measured anti-drug antibodies in the healthy volunteer studies, in patients treated with oral or parenteral defibrotide for thrombotic disorders, or in patients with VOD treated with intravenous defibrotide, please identify where in the NDA the results are located. If you have conducted no immunogenicity studies in humans, provide justification for not having performed such studies.

Please respond by **noon, Friday, Oct. 30, 2015 EST.** Please reply by e-mail to Beatrice and me in addition to submitting an official submission to your NDA.

Please confirm receipt of this email.

Sincerely,

Janet on behalf of Beatrice Kallungal

Janet G. Higgins
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2389
Silver Spring, MD 20903

(240) 402-0330 (phone)
(301) 796-9845 (fax)

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/s/

JANET G HIGGINS
10/26/2015

From:	Kallungal, Beatrice
To:	Robin Hume
Cc:	Kallungal, Beatrice
Subject:	NDA 208114, Defibrotide - Information Request _10/23/2015
Date:	Friday, October 23, 2015 3:15:37 PM

Hello,
Please find below the information request for NDA 208114. Please submit your response to this request via e-mail by **4 pm EDT Monday October 26 , 2015** followed by officially submitting the response to the NDA.

- *Please explain why N=75 was used for 25 mg/kg , instead of N=72 as shown if the* (b) (4) *was specified in SAS code for study 99-118.*

Please acknowledge receipt of this request.

Regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
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/s/

BEATRICE A KALLUNGAL
10/23/2015

From:	Patel, Soumya
To:	robin.hume@jazzpharma.com
Cc:	Kallungal, Beatrice; Startzman, Henry
Subject:	Rare Pediatric Disease Voucher Request for Hepatic Veno-Occlusive Disease with (b) (4) Dysfunction following HSCT
Date:	Thursday, October 22, 2015 8:55:23 AM

Dear Robin,

We in the Office of Orphan Products Development were consulted by the Division of Hematology Products regarding Gentium S.p.A.'s request for a Rare Pediatric Disease Voucher for defibrotide for the treatment of hepatic veno-occlusive disease (VOD) with (b) (4) dysfunction (MOD) following hematopoietic stem-cell transplantation (HSCT). We were consulted in an effort to determine whether the disease is a rare pediatric disease.

While you have requested a Rare Pediatric Disease Voucher for hepatic VOD with (b) (4) following HSCT, we believe that the disease at hand is hepatic VOD. Unless there is some feature or characteristic (e.g., mechanism of action, toxicity profile) of your product that would limit its use to only patients with hepatic VOD with (b) (4) following HSCT, the entire hepatic VOD population, regardless of etiology, must be accounted for in your population estimate calculation. As you are aware, hepatic VOD may be due to various conditions outside of the HSCT population (e.g., patients on chemotherapeutics given at more conventional doses as well as those on chronic immunosuppression; patients who are post liver transplantation, or who suffer from Wilms tumor, neuroblastoma etc). Unless you can provide additional information as to why your product must be restricted to only a subset of hepatic VOD patients, you would have to take into consideration all cases of hepatic VOD that occur in a given year regardless of etiology and demonstrate that >50% of the incident cases of hepatic VOD occur in those 0 through 18 years of age. While you note that hepatic VOD with (b) (4) following HSCT occurs more often in pediatric patients, an Emedicine article (please see emedicine.medscape.com/article/989167-overview#a6) notes that the incidence of hepatic VOD following HSCT ranges from 5-60% in children and that similar rates have been reported in adults.

Please provide further information that indicates that there is some feature of your product that limits its use to only a subset of hepatic VOD cases (those with hepatic VOD with (b) (4) following HSCT) or please provide a revised population estimate calculation that includes all patients with hepatic VOD in a given year regardless of etiology and that demonstrates that hepatic VOD is a rare pediatric disease.

Thank you.

Soumya Patel, Pharm.D.
Health Science Administrator
FDA/OOPD

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/s/

BEATRICE A KALLUNGAL
10/22/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208114

INFORMATION REQUEST

Gentium S.p.A (Jazz Pharmaceuticals, Inc.)
Attention: Robin L. Hume
Director of Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Hume:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for defibrotide.

We also refer to your July 31, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The designation of the intermediate, (b) (4) as an API starting material is not acceptable. To be consistent with other similarly derived APIs, (b) (4) may be considered as the starting material for defibrotide.

2. Provide information regarding potential genotoxic/carcinogenic impurities that might arise from starting materials, intermediates, and known/potential impurities and degradants of defibrotide synthesis.

3. Identify the drug substance batch from which the current reference standard (CRM 346/00/12) was obtained.

4. Provide updated structural characterization data/spectra for the current drug substance reference standard (CRM 346/00/12) including a Certificate of Analysis. The structural characterization data submitted in the NDA for defibrotide reference standard was obtained from the previous reference standard (CRM 025/00/06).

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by November 10, 2015.

Sincerely,

Digitally signed by Janice T. Brown -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300101685, cn=Janice T. Brown -A
Date: 2015.10.20 13:41:52 -04'00'

Janice Brown, M.S.
Quality Assessment Lead, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208114

INFORMATION REQUEST

Gentium S.p.A (Jazz Pharmaceuticals, Inc.)
Attention: Robin L. Hume
Director of Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Hume:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for defibrotide.

We also refer to your July 31, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Submit an English translation of the executed batch records for the Defibrotide injection drug product, 80 mg/mL.

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by October 19, 2015.

Sincerely,

Digitally signed by Janice T. Brown -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300101685, cn=Janice T. Brown -A
Date: 2015.10.05 19:26:08 -04'00'

Janice Brown, M.S.
Quality Assessment Lead, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From:	Kallungal, Beatrice
To:	Robin Hume
Cc:	Kallungal, Beatrice
Subject:	NDA 208114, Defibrotide - Information Request _10/01/2015
Date:	Thursday, October 01, 2015 1:41:14 PM

Hello,
Please find below the information request for NDA 208114. Please submit your response to this request via e-mail by **4 pm EDT Wednesday October 7, 2015** followed by officially submitting the response to the NDA.

- *Submit the following study subject data listing information grouped as pdf files, sorted separately by the three requested clinical study sites, for Paul Richardson, MD (Site 01), Angela Smith, MD, MS (Site 11), and Nancy Kernan, MD (Site 08), under Study Protocol 2005-01.*
  a) Subject discontinuations (If applicable per treatment group: site, subject number, screening visit date, randomization date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation).
  b) Subject assignment per treatment arm (as applicable).
  c) Primary study efficacy endpoint.
  d) Concomitant medication list (non-study medications).
  e) All adverse events (If applicable, per treatment group: preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event (SAE [yes/no], death [yes/no]).

- *Submit all versions of the informed consent form documents in Study Protocol 2005-01.*

Please acknowledge receipt of this request.

Regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
10/01/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208114

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Gentium S.p.A.
c/o Jazz Pharmaceuticals, Inc.
Attention: Robin Hume, MS, RAC
Director, Regulatory Affairs, US Agent
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Hume:

Please refer to your New Drug Application (NDA) dated July 30, 2015, received July 31, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Defibrotide solution for infusion, 200 mg/2.5mL.

We also refer to your amendments dated August 6, 28, September 21, 23, 24, and 25, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is March 31, 2016. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by January 2, 2016.

In addition, the planned date for our internal mid-cycle review meeting is November 10, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
09/29/2015

From:	Kallungal, Beatrice
To:	Robin Hume
Cc:	Kallungal, Beatrice
Subject:	NDA 208114, Defibrotide - Information Request _ 09/17/2015
Date:	Thursday, September 17, 2015 11:51:33 AM

Hello,
Please find below the information request for NDA 208114. Please submit your response to this request via e-mail by **4 pm EDT Wednesday September 23, 2015** (unless otherwise indicated below) followed by officially submitting the response to the NDA.

- *Provide the project file (.phxproj) which was used for the population PK analyses and simulations. The project file should include all the relevant analyses/plot/diagnostics for key models (base, covariate, final model etc.) reported in the population PK Report (Protocols: DF VOD-2012-03-PKRen, R09-1425 and 99-118). Please submit the project file through e-mail if feasible and then follow up with a formal submission through CD.* ***Provide a response by 3 pm EDT September 21, 2015****.*

- *In Table 1 of the proposed prescribing information,* (b) (4) [redacted]

- *Please submit contact information(addresses, phone numbers, fax and emails) for the following sites from Study 2005-01:*
  - *University of Michigan Cancer Center*
  - *Oregon Health and Science University*
  - *Memorial Sloan-Kettering Cancer Center*
  - *Fred Hutchinson Cancer Research Center*
  - *Duke University Medical Center*
  - *City of Hope Medical Center*
  - *Dana-Farber Cancer Institute*
  - *MD Anderson Cancer Center*
  - *Stanford University Medical Center*
  - *University of Minnesota Medical Center*

Please acknowledge receipt of this request.

Regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager

Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
09/17/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 062118
NDA 208114

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Gentium, S.p.A.
c/o Jazz Pharmaceuticals, Inc.
3180 Porter Drive
Palo Alto, CA 94304

ATTENTION: Robin L. Hume
Director of Regulatory Affairs

Dear Ms. Hume:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act, and your New Drug Application (NDA) dated and received July 31, 2015, submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for Defibrotide Solution for Infusion, 200 mg/2.5 mL.

We also refer to:

- Your correspondence to your IND, dated and received March 27, 2015, requesting review of your proposed proprietary name, Defitelio
- Your correspondence to your NDA, dated and received July 31, 2015, requesting review of your proposed proprietary name, Defitelio

We have completed our review of the proposed proprietary name, Defitelio and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sarah Harris, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4774. For any other information regarding this application, contact Beatrice Kallungal, Regulatory Project Manager in the Office of New Drugs, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
09/15/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208114

NDA ACKNOWLEDGMENT

Gentium S.p.A.
c/o Jazz Pharmaceuticals, Inc.
Attention: Robin Hume, MS, RAC
Director, Regulatory Affairs, US Agent
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Hume:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Defibrotide Solution for infusion, 200 mg/2.5mL

Date of Application: July 30, 2015

Date of Receipt: July 31, 2015

Our Reference Number: NDA 208114

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 29, 2015 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Beatrice Kallungal, BS
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

BEATRICE A KALLUNGAL
08/07/2015

Laiq, Rabiya

From: Laiq, Rabiya
Sent: Tuesday, August 04, 2015 12:59 AM
To: 'robin.hume@jazzpharma.com'
Cc: Kallungal, Beatrice
Subject: FDA Information Request NDA 208114- Please Respond by September 1, 2015.

Dear Ms. Hume,

My name is Rabiya Laiq, I will be your point of contact for all CMC inquiries. We are reviewing your application and have the following information requests.

Please provide the following information or a reference to its location in the subject submission.

1. We refer to Module 3.2.P.2.5. Provide a summary of the microbial immersion test method to support the proposed commercial container. Include a description of the bacterial suspension(s), the (b) (4) time, the positive and negative controls, the incubation time, and a description of any (b) (4) conditions utilized.

2. Provide a description of the air classification for the rooms containing (b) (4) Include a description, if applicable, of how critical sterile components (b) (4)

3. Provide a summary of the acceptance criteria (alert and action levels) for the environmental monitoring program.

4. We refer to Module 3.2.P.3.5 page 46/50. (b) (4) All commercial (b) (4) should be supported with adequate bacterial challenge studies.

5. We acknowledge the (b) (4) results from 2003 presented in Module 3.2.P.3.5.2.4. Provide a summary of recent (b) (4) studies.

6. Clarify which (b) (4) are utilized for (b) (4) and indicate which validation studies were conducted in each (b) (4) Include validation data to support the (b) (4) in all commercial (b) (4)s or provide a rationale for why studies conducted in one (b) (4) are applicable to other (b) (4)

7. We refer to the (b) (4)) included in (b) (4) studies. (b) (4) incubation time and temperature for control and test BIs.

8. We refer to the (b) (4) studies in Module 3.2.P.3.5. Clarify the following:
   a. Indicate whether both (b) (4) µm (b) (4) are included during (b) (4). We refer to Figure 10 for additional information. Figure 10 only includes a single (b) (4) µm (b) (4) (b) (4)

   b. Describe what is meant on page 34/50 by (b) (4)

   c. Module 3.2.P.3.5.4.4 states that "Any failure to comply with the critical process parameters during routine (b) (4) Provide these critical process parameters.

9. We refer to the [redacted] conducted on [redacted] and described in Module 3.2.P.3.5 (page 5/50). According to Module 3.2.A.1.3, the proposed [redacted]. Please clarify how the submitted [redacted] are applicable to the [redacted]. Alternately, provide a summary of the methods and results from [redacted] conducted with the proposed commercial equipment in Sterile 2.

10. Provide a summary of actions to occur should a [redacted] fail. Include a brief description of the investigation and the disposition of [redacted].

11. Provide a summary of the sterility and endotoxin test method verification studies and results. We refer to R-QCB-239 and R-QCB-241 for more information.

Please feel free to contact me for any clarification or questions.

Kindly confirm receipt of this email.

Please send the responses to myself via email followed by a formal submission though the gateway by September 1, 2015 or sooner.

Thanks,
Rabiya

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov

From:	Kallungal, Beatrice
To:	Robin Hume
Cc:	Kallungal, Beatrice
Subject:	NDA 208114, Defibrotide - Information Request
Date:	Tuesday, July 21, 2015 4:08:13 PM

Hi Robin,
Please find below the information request for NDA 208114. Please submit your response to this request via e-mail **by 4 pm EDT Tuesday July 28, 2015** followed by officially submitting the response to the NDA.

We note that you submitted a request for proprietary name review to IND 062118 on March 27, 2015. If you plan to request this name for your NDA, we recommend you formally submit the request for proprietary name review to the NDA at this time. Please refer to the guidance below for instructions on a complete submission.

Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

Please acknowledge receipt of this request.

Regards,

Beatrice

Beatrice Kallungal
Senior Regulatory Health Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
WO22, Room 2354
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-9304 (phone)
(301) 796-9845 (fax)
E-Mail: beatrice.kallungal@fda.hhs.gov

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/s/

BEATRICE A KALLUNGAL
07/21/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 062118

MEETING MINUTES

Gentium S.p.A.
c/o Jazz Pharmaceuticals, Inc.
Attention: Robin Hume, MS, RAC
Director of Regulatory Affairs, US Agent
40 Worth Street, 10th Floor
New York, NY 10013

Dear Ms. Hume:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for defibrotide.

We also refer to the meeting between representatives of your firm and the FDA on August 21, 2014. The purpose of the meeting was to discuss the clinical and nonclinical data to be included in the defibrotide New Drug Application resubmission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	August 21, 2014, 2:00 PM – 3:00 PM EDT
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1421 Silver Spring, Maryland 20903
Application Number:	IND 062118
Product Name:	Defibrotide
Indication:	For the treatment of (b) (4) hepatic veno-occlusive disease (VOD) following hematopoietic stem cell transplantation (HSCT) therapy
Sponsor/Applicant Name:	Gentium S.p.A.
Meeting Chair:	R. Angelo de Claro, MD
Meeting Recorder:	Beatrice Kallungal, BS

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)
Gregory Reaman, MD, Associate Director for Oncology Sciences
Paul Kluetz, MD, Deputy Director (Acting)

Division of Hematology Products
Ann Farrell, MD, Director
Edvardas Kaminskas, MD, Deputy Director
Donna Przepiorka, MD, PhD, Clinical Reviewer
Tanya Wroblewski, MD, Clinical Reviewer
Nicole Verdun, MD, Medical Officer
R. Angelo de Claro, MD, Clinical Team Leader
Beatrice Kallungal, BS, Regulatory Project Manager
Amy Baird, Chief of Project Management Staff

Division of Hematology Oncology Toxicology
Shwu-Luan Lee, PhD, Reviewer
Brenda Gehrke, PhD, Reviewer

Office of Clinical Pharmacology
Joseph Grillo, PharmD, Reviewer

Office of Biostatistics
Yuan-Li Shen, PhD, Team Leader
Xin Gao, PhD, Reviewer

Office of New Drug Quality Assessment
Janice Brown, MS, CMC Lead

EASTERN RESEARCH GROUP ATTENDEES
Christopher Sese, Independent Assessor

SPONSOR ATTENDEES
Krishna Allamneni, DVM, PhD, DABT, Executive Director, Nonclinical Development, Jazz
David Borbas, RN, MIS, Senior Director, Data Management, Jazz
Jennifer Ekelund, Vice President, United States Regulatory Affairs, Jazz
Mark Eller, PhD, Head of Early Stage Development, Research and Pharmacology, Jazz
Frederic Godderis, MSc, Global Head of Research and Development Operations, Jazz
(b) (4)
Robin Hume, MS, RAC, Director, Regulatory Affairs, Jazz/ United States Agent for Gentium
Chinglin Lai, PhD, Vice President, Biostatistics and Data Management, Jazz
Charles LaPree, MS, Head of Global Regulatory Affairs, Jazz
John Miller, Project Team Lead, Commercial Management, Jazz
Maja Miloslavsky, PhD, Director, Biostatistics, Jazz
Bijan Nejadnik, MD, Executive Director, Medical Affairs, Jazz
Joel Selcher, PhD, Head of United States Regulatory Strategy, Jazz

1.0 BACKGROUND

On June 30, 2011, Gentium submitted a New Drug Application (NDA) for defibrotide and met with the Agency in an application orientation meeting. Based on issues related to the clinical data that were identified during the review of the application, Gentium withdrew the NDA on August 17, 2011.

On November 12, 2013, Gentium submitted a Type B Pre-NDA meeting package to the Agency and received the preliminary meeting comments on December 4, 2013. Subsequently, Gentium withdrew the meeting request to allow time for evaluation of the Agency's comments and to allow for a future pre-NDA meeting to discuss open issues.

On April 8, 2014, the Sponsor met with the Agency to discuss critical issues within the preamble of the Preliminary Comments received on December 4, 2013. The Sponsor and the Agency also discussed the data to include in the NDA submission to address critical concerns with the 2005-01 Historical Control group.

The purpose of this pre-NDA meeting is to provide Sponsor feedback and to discuss the Sponsor's approach in addressing previous FDA comments to support an NDA for defibrotide for the above stated indication.

2. DISCUSSION

General question:

Q1 Does the Agency agree with the Sponsor's proposed responses and plan for submitting the requested data as detailed in a point-by-point response and supported by the data submission plan as well as other documents included in this meeting package?

FDA Response:

Your proposed approach and data submission plan appears reasonable. The Agency will determine the acceptability of the data for filing and review at the time of the NDA submission.

Be certain that you include the prognostic information for the 37 Historical Control patients (Group C) for whom data is available in addition to all of their baseline variables and screening/inclusion/exclusion.

In your resubmission, also please be sure that all issues raised in our August 30, 2011 letter acknowledging your NDA withdrawal, have been fully addressed**.** Also include the protocol and statistical analysis plan (SAP) (original and all amended versions) for the experimental arm and historical control selection in the NDA submission. In addition, include and summarize all correspondence (written documents or meeting minutes) with FDA in regard to protocol and SAP for study 2005-001, Data and Safety Monitoring Board (DSMB) meeting minutes/reports and the important dates during the development (i.e., database lock date, interim analyses or interim locked dates for the DSMB, all version of SAP sign-off dates, all version of protocol sign-off dates, etc.).

Please provide timelines of when the patient selections were made and ensure that they were made without knowing the efficacy results. For further comments, please refer to the Agency's responses to Question 2 to Question 9.

Meeting discussion:

No discussion occurred.

Clinical questions:

Q2 Does the Agency agree that the proposed analyses, together with the datasets to be provided for the 2005-01 study in the NDA, are adequate to address the Agency's requests related to this study?

FDA Response:

Your proposal not to submit the patients in Group C is not acceptable. Please submit the efficacy variables (primary and major secondary efficacy endpoints) and important prognostic variables for all three groups (Group A, B, and C) in both SDTM and ADaM formats in the application.

Please summarize the algorithm with detailed information which was used to select the final group of historical control patients (Group A) in the submission. The datasets need to include all 123 patients (Group A + B + C defined in your package) in both SDTM and ADaM formats in your NDA submission.

Please note that all important prognostic variables besides the four variables which will be used in the propensity score model should be included in the submission.

The Agency reiterates that the number of patients with missing efficacy variables and important prognostic variables should be kept to minimum. Too much missing data will lead to both filing and review issues. Please note that not having sufficient data will hinder the ability for the Agency to do a thorough review for your submission.

The acceptability of the data for filing and review will be determined at the time of submission.

Meeting discussion:
The baseline data proposed by the Sponsor for groups A, B, and C is acceptable. Efficacy data will be provided for the primary and secondary endpoint for group A, for the primary efficacy endpoint for day 100 survival and day 180 survival for group B, and no efficacy data will be provided for group C. The Agency recommended that the Sponsor include documentation of methods and efforts used to collect all available efficacy data.

Q3 Does the Agency agree with the proposed approach to sensitivity analyses?

FDA Response:
You did not provide sufficient information for the Agency to evaluate your proposed sensitivity analysis, as details for the selection of variables and missing data handling strategy for logistic models in deriving the propensity score are not described in the SAP.

Meeting discussion:
FDA acknowledges the Sponsor's response regarding the approach to the sensitivity analysis. FDA requests that the sensitivity analysis should be performed based on 86 patients versus 102, as referenced in section 10.3.3 of the SAP. Additional sensitivity analyses including the nine prognostic variables in propensity score model is requested by the Agency. The Agency requested that the Sponsor explain any differing results across the sensitivity analyses.

Q4 Does the Agency agree that the Sponsor's plan for submission and analysis of the 2006-05 study data is acceptable given that the data may be incomplete and the overall quality of data is expected to be adversely impacted by the lack of source data verification for this study?

FDA Response:
Your plan for submission and analysis for Study 2006-05 is acceptable. Given that the data may be incomplete, the extent to which the data from Study 2006-05 will be able to be used as supportive data in the review process will be determined at time of the submission**.**

Meeting discussion:
No discussion occurred.

Q5 Does the Agency agree with the Sponsor's proposed plans for efficacy analyses, data submission, and population definitions for the 2006-05 clinical study?

FDA Response:
Yes. Your proposed efficacy analyses, data submission and population definitions in 2006-05 appear to be reasonable for a submission. We will determine the acceptability of the data for filing and review at the time of the NDA submission.

Meeting discussion:
No discussion occurred.

Q6 Does the Agency agree that the information provided regarding the Center for International Blood and Marrow Transplant Research study is adequate to support filing of the defibrotide NDA?

FDA Response:
We recommend adding the following questions from the CIBMTR forms to your datasets:

- Q229: Date of acute GVHD diagnosis
- Q249: Was specific therapy used to treat acute GVHD
- Q250-274(specify therapy used to treat acute GVHD)
- Q434, 443, 452, 461: (further details regarding non-infectious pulmonary abnormalities other than Ipn, IPS, ARDS)
- Q463: Did the recipient receive endotracheal intubation or mechanical ventilation post-HSCT?
- Q465: Date of diagnosis of liver toxicity
- Q471: Maximum bilirubin in first 100 days
- Q475: ascites
- Q477: bilirubin > 2.0mg
- Q479: Elevated hepatic venous pressure gradient
- Q480: Elevated liver enzymes
- Q481: Hepatomegaly
- Q482: Right upper quadrant pain or tenderness
- Q483: Ultrasonography/Doppler(abnormal portal vein flow)
- Q484: weight gain> 5%
- Q485: Other(specify finding)
- Q511: renal failure sever enough to warrant dialysis
- Q513: Did recipient receive dialysis

Please submit analyses datasets, in addition to raw datasets, for all variables used in the primary and secondary efficacy endpoint analyses, sensitivity analyses, and all variables used in the

safety analyses. Also include the protocol and statistical analysis plan (original and all amended versions) for defibrotide treated and non-treated groups in the NDA submission.

Meeting discussion:
The Sponsor commits to discuss with CIBMTR regarding the additional variables requested by the Agency. The Sponsor will provide an update to the Agency regarding the availability of the above data for the 96 patients. The Agency agrees with the Sponsor's proposal to include any available data in the datasets. The Sponsor agrees to provide the ADaM data. The Agency understands there is no protocol.

Q7 Does the Agency agree to the study-specific populations proposed for the datasets and analyses included within the Integrated Summary of Efficacy?

FDA Response:
Yes. The study-specific populations for datasets and analyses proposed for the ISE appear reasonable.

Meeting discussion:
No discussion occurred.

Q8 Does the Agency agree with the Sponsor's planned endpoints for the Integrated Summary of Efficacy?

FDA Response:
Yes. Your planned main endpoint of patient survival at Day + 100 post HSCT is acceptable. We recommend that you also include an integrated analysis of overall survival and complete response where data are available.

Meeting discussion:
No discussion occurred.

Q9 Does the Agency agree to the Sponsor's proposed integration of studies for the safety analyses in the Integrated Summary of Safety?

FDA Response:
Yes.

Meeting discussion:
No discussion occurred.

Clinical pharmacology question:
Q10 Does the Agency agree that the Sponsor's proposed plan for providing clinical pharmacology data in the NDA is acceptable for filing the defibrotide NDA?

FDA Response:
No. You should supply datasets for all of the clinical pharmacology trials you intend to submit in support of your application. Based on your previous submissions to the Agency this includes, but is not necessarily limited to, trials IRI-151612, DFPK88, DFPK 99-118, DFPK91, R09-1425, (b) (4)

(b) (4)

Meeting discussion:
The Sponsor should submit the final study report and the respective datasets as hard copy or electronic datasets. The Agency recommends the hard copy of sufficient quality to allow for navigation through the document and other document functions, including text recognition.

Nonclinical questions:
Q11 Assuming the results of the embryofetal developmental toxicity study in rabbits and the genotoxicity studies are acceptable, does the Agency agree that no additional toxicology studies are required for filing the defibrotide NDA?

FDA Response:
The type of studies are acceptable for filing; however, as mentioned in the comments sent in December 2013, some of the toxicology studies required for the NDA are either non-GLP or confounded. The decision on whether or not the studies are adequate for filing the NDA will be made once the NDA is submitted and the studies, GLP deviations, and supportive information are considered.

Meeting discussion:
No discussion occurred.

Q12 Does the Agency agree with the Sponsor's proposed plan to address the GLP status of the toxicology reports?

FDA Response:
Yes. Your plan (to include the GLP status for all studies, deviations from GLP, and an assessment of the impact on the interpretation of the results) is acceptable. Whether or not the submitted studies are acceptable and whether additional studies are needed will be a review issue.

Meeting discussion:
No discussion occurred.

(b) (4)

FDA Response:

(b) (4)

Meeting discussion:
No discussion occurred.

Additional Comments:

- We recommend that you explore the feasibility of additional prospective randomized clinical trials to support your application. A randomized early intervention trial is one possibility you may want to consider. We recommend that you submit a synopsis of any future protocols you may be considering.

- Please include the SAS programs used to derive the primary and key secondary efficacy endpoints from the SDTM data. SAS programs used for the primary and key secondary efficacy endpoints analyses based on ADaM data and for any new results included in the proposed labeling should also be included. Note that these SAS programs need to include all pivotal and supportive studies with efficacy findings.

Meeting discussion:
No discussion occurred.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed.

- The Agency and the Sponsor discussed the proposed NDA submission and reached agreement on the definition of a complete NDA submission. The Sponsor will provide a proposal including timeline and complete table of contents for a rolling submission.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that at this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. We will determine the need for a REMS and the required elements during the review of your application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. The Sponsor stated

that they intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting was held on August 7, 2014. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation

conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were not action items from this meeting.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's response to the Agency's preliminary meeting comments is appended to the meeting minutes.

Meeting Questions:

General question:

Q1 Does the Agency agree with the Sponsor's proposed responses and plan for submitting the requested data as detailed in a point-by-point response and supported by the data submission plan as well as other documents included in this meeting package?

FDA Response:

Your proposed approach and data submission plan appears reasonable. The Agency will determine the acceptability of the data for filing and review at the time of the NDA submission. Be certain that you include the prognostic information for the 37 Historical Control patients (Group C) for whom data is available in addition to all of their baseline variables and screening/inclusion/exclusion.

In your resubmission, also please be sure that all issues raised in our August 30, 2011 letter acknowledging your NDA withdrawal, have been fully addressed**.** Also include the protocol and statistical analysis plan (original and all amended versions) for the experimental arm and historical control selection in the NDA submission. In addition, include and summarize all correspondence (written documents or meeting minutes) with FDA in regard to protocol and SAP for study 2005-001, Data safety monitoring board (DSMB) meeting minutes/reports and the important dates during the development (i.e., database lock date, interim analyses or interim locked dates for the DSMB, all version of SAP sign-off dates, all version of protocol sign-off dates, etc.).

Please provide timelines of when the patient selections were made and ensure that they were made without knowing the efficacy results. For further comments, please refer to the Agency's responses to Question 2 to Question 9.

Sponsor Response/ Meeting Discussion

No discussion needed.

Clinical questions:

Q2 Does the Agency agree that the proposed analyses, together with the datasets to be provided for the 2005-01 study in the NDA, are adequate to address the Agency's requests related to this study?

FDA Response:

Your proposal not to submit the patients in Group C is not acceptable. Please submit the efficacy variables (primary and major secondary efficacy endpoints) and important prognostic variables for all three groups (Group A, B, and C) in both SDTM and ADaM formats in the application. Please summarize the algorithm with detailed information which was used to select the final group of historical control patients (Group A) in the submission. The datasets need to include all 123 patients (Group A + B + C defined in your package) in both SDTM and ADaM formats in your NDA submission.

Please note that all important prognostic variables besides the four variables which will be used in the propensity score model should be included in the submission.

The Agency reiterates that the number of patients with missing efficacy variables and important prognostic variables should be kept to minimum. Too much missing data will lead to both filing and review issues. Please note that not having sufficient data will hinder the ability for the Agency to do a thorough review for your submission. The acceptability of the data for filing and review will be determined at the time of submission.

Sponsor Response/ Meeting Discussion

The Sponsor plans to submit all of the available data from the patients included in Group C (N=37) including entry data, stratification variables, and other important baseline prognostic variables as listed in the SAP (Section 10.2). We expect minimal missing information for baseline and prognostic variables for the 123 patients (Groups A, B and C).

We are following the Agency advice from December 2013 and April 2014 regarding the submission of efficacy data in the NDA. Efficacy variables will be submitted for Groups A, B as available. For Group A (N=32) we will submit all primary and major secondary endpoint variables.

Group B (N=54) available efficacy data includes the primary efficacy endpoint (Day+ 100 survival). Due to the lack of raw data, an assessment of CR according to the Agency- defined criteria is not possible for Group B. The Sponsor maintains that by providing efficacy narratives as discussed and agreed with the Agency in April 2014, the Agency would be able to assess the outcome of these patients based on the data currently available.

As discussed with the Agency in April 2014, the 2005-01 study design and conduct was such that collection of outcome data, including efficacy data, was not performed and case report forms were not completed until the MRC identified a historical control patient as eligible. Because the patients in Group C (N=37) were never selected as meeting a diagnosis of severe VOD, the outcome data were not collected. Therefore, efficacy data for patients in Group C (N=37) are not available to submit.

Q3 Does the Agency agree with the proposed approach to sensitivity analyses?

FDA Response:
You did not provide sufficient information for the Agency to evaluate your proposed sensitivity analysis, as details for the selection of variables and missing data handling strategy for logistic models in deriving the propensity score are not described in the SAP.

Sponsor Response/ Meeting Discussion
There are two types of sensitivity analyses considered in the 2005-01 SAP:

1. *Sensitivity analysis of the propensity score stratified Koch weighted analysis will be undertaken by examining additional potential prognostic variables and their effect on efficacy endpoints of interest as specified in section 10.2 of the SAP*
   - *Unadjusted analysis will be presented for the efficacy endpoints of interest (Day+100 survival and Complete Response) by the subgroups defined by all potential prognostic variables specified in the SAP*
   - *Propensity score stratified Koch weighted analysis will be presented with the propensity score defined by the logistic model including the 4 baseline prognostic factors plus all the additional potential prognostic variables specified in the SAP. There is no missing data anticipated in the values of prognostic or potential prognostic variables for the 102 Defibrotide treated or 32 Historical Control patients.*
2. *We would like to propose the removal of the sensitivity analysis of Day +100 Survival as described in section 10.3.3 of the SAP specifying the inclusion of additional 54 patients into the Historical Control group. We do not support this analysis as a meaningful evaluation of efficacy since the patients included in the group of 54 were not considered to have an unequivocal diagnosis of hepatic VOD with associated organ failure.*

We would like to proceed to finalize the SAP with the above clarification of sensitivity analysis considering additional potential prognostic factors and the removal of the sensitivity analysis including the additional 54 patients into the Historical Control.

Q4 Does the Agency agree that the Sponsor's plan for submission and analysis of the 2006-05 study data is acceptable given that the data may be incomplete and the overall quality of data is expected to be adversely impacted by the lack of source data verification for this study?

FDA Response:
Your plan for submission and analysis for Study 2006-05 is acceptable. Given that the data may be incomplete, the extent to which the data from Study 2006-05 will be able to be used as supportive data in the review process will be determined at time of the submission**.**

Sponsor Response/ Meeting Discussion
No discussion needed.

Q5 Does the Agency agree with the Sponsor's proposed plans for efficacy analyses, data submission, and population definitions for the 2006-05 clinical study?

FDA Response:
Yes. Your proposed efficacy analyses, data submission and population definitions in 2006-05 appear to be reasonable for a submission. We will determine the acceptability of the data for filing and review at the time of the NDA submission.

Sponsor Response/ Meeting Discussion
No discussion needed.

Q6 Does the Agency agree that the information provided regarding the Center for International Blood and Marrow Transplant Research study is adequate to support filing of the defibrotide NDA?

FDA Response:
We recommend adding the following questions from the CIBMTR forms to your datasets:
☐ Q229: Date of acute GVHD diagnosis
☐ Q249: Was specific therapy used to treat acute GVHD
☐ Q250-274(specify therapy used to treat acute GVHD)
☐ Q434, 443, 452, 461: (further details regarding non-infectious pulmonary abnormalities other than Ipn, IPS, ARDS)
☐ Q463: Did the recipient receive endotracheal intubation or mechanical ventilation post-HSCT?
☐ Q465: Date of diagnosis of liver toxicity
☐ Q471: Maximum bilirubin in first 100 days
☐ Q475: ascites
☐ Q477: bilirubin > 2.0mg
☐ Q479: Elevated hepatic venous pressure gradient
☐ Q480: Elevated liver enzymes
☐ Q481: Hepatomegaly
☐ Q482: Right upper quadrant pain or tenderness
☐ Q483: Ultrasonography/Doppler(abnormal portal vein flow)
☐ Q484: weight gain> 5%
☐ Q485: Other(specify finding)
☐ Q511: renal failure sever enough to warrant dialysis
☐ Q513: Did recipient receive dialysis

Please submit analyses datasets, in addition to raw datasets, for all variables used in the primary and secondary efficacy endpoint analyses, sensitivity analyses, and all variables used in the safety analyses. Also include the protocol and statistical analysis plan (original and all amended versions) for Defibrotide treated and non-treated groups in the NDA submission.

Sponsor Response/ Meeting Discussion
Datasets will be submitted as requested and outlined in the Dataset Submission Plan provided with the pre-NDA Meeting Package. The Sponsor will submit all versions of the statistical analysis plan finalized for the analyses included within the NDA. As a point of clarification, there was no protocol for this registry dataset

The Sponsor will evaluate with CIBMTR the data requested and provide datasets as available for the 96 patients selected as having a diagnosis of severe VOD and included in the analysis.

Q7 Does the Agency agree to the study-specific populations proposed for the datasets and analyses included within the Integrated Summary of Efficacy?

FDA Response:
Yes. The study-specific populations for datasets and analyses proposed for the ISE appear reasonable.

Sponsor Response/ Meeting Discussion
No discussion needed.

Q8 Does the Agency agree with the Sponsor's planned endpoints for the Integrated Summary of Efficacy?

FDA Response:
Yes. Your planned main endpoint of patient survival at Day + 100 post HSCT is acceptable. We recommend that you also include an integrated analysis of overall survival and complete response where data are available.

Sponsor Response/ Meeting Discussion
No discussion needed.

Q9 Does the Agency agree to the Sponsor's proposed integration of studies for the safety analyses in the Integrated Summary of Safety?

FDA Response:
Yes.

Sponsor Response/ Meeting Discussion
No discussion needed.

Clinical pharmacology question:

Q10 Does the Agency agree that the Sponsor's proposed plan for providing clinical pharmacology data in the NDA is acceptable for filing the defibrotide NDA?

FDA Response:
No. You should supply datasets for all of the clinical pharmacology trials you intend to submit in support of your application. Based on your previous submissions to the Agency this includes, but is not necessarily limited to, trials IRI-151612, DFPK88, DFPK 99-118, DFPK91, R09-1425, GENT-PCS-100, CS001/03, and DF-VOD-2012-03PK-REN (b) (4)
(b) (4)

Sponsor Response/ Meeting Discussion
Studies IRI-151612, DFPK88, CS001/03 and DFPK91 were conducted in the late 1980's and early 1990's. There are no electronic data sets for these studies. Additionally, the bioanalytical methods used to support these studies were not validated or the validation status cannot be determined. These studies provide information of limited usefulness to characterize the pharmacokinetics of defibrotide in light of the data collected in the other studies and given the current proposed indication and route of administration. For example, they focus on PO vs IV pharmacokinetics / bioavailability (DFPK88, DFPK91), disposition of I-125 labeled defibrotide (IRI-151612), and pharmacodynamics in patients with chronic peripheral artery disease (CS001/03). We propose to include these reports for completeness; including them with literature data from peer reviewed journals. (b) (4)
.

Full electronic data sets will be provided for studies DFPK 99-118, R09-1425 and DF-VOD-2012-03PK-REN which used validated bioanalytical methods. Full electronic data sets will also be provided for the population PK analysis of the pooled data from these studies, GENT-PSC-100. These studies will be used to characterize the human pharmacokinetics of defibrotide. They contain data on patients undergoing treatment for VOD, healthy subjects, as well as subjects with diseases of the main drug eliminating organs (renal patients, and patients with hepatic impairment due to the underlying disease being treated). The doses studied include single and multiple doses as well as the proposed clinical and supra-therapeutic doses (QTc study, R09-1425). Therefore, we believe these studies are sufficient to characterize the clinical pharmacokinetics of defibrotide without relying on the historic studies described above.

Nonclinical questions:

Q11 Assuming the results of the embryofetal developmental toxicity study in rabbits and the genotoxicity studies are acceptable, does the Agency agree that no additional toxicology studies are required for filing the defibrotide NDA?

FDA Response:
The type of studies are acceptable for filing; however, as mentioned in the comments sent in December 2013, some of the toxicology studies required for the NDA are either non-GLP or confounded. The decision on whether or not the studies are adequate for filing the NDA will be made once the NDA is submitted and the studies, GLP deviations, and supportive information are considered.

Sponsor Response/ Meeting Discussion
No discussion needed. The Sponsor respectfully acknowledges the FDA response and thanks the FDA for affirming that the adequacy of the toxicology studies will be a review issue. The Sponsor notes that this is consistent with the FDA response to Question 12 in the December 2013 Preliminary Responses, which indicated that during the NDA review, a determination will be made on whether or not any additional nonclinical studies that need to be conducted, will be post-marketing requirements.

Q12 Does the Agency agree with the Sponsor's proposed plan to address the GLP status of the toxicology reports?

FDA Response:
Yes. Your plan (to include the GLP status for all studies, deviations from GLP, and an assessment of the impact on the interpretation of the results) is acceptable. Whether or not the submitted studies are acceptable and whether additional studies are needed will be a review issue.

Sponsor Response/ Meeting Discussion
No discussion needed. The Sponsor respectfully acknowledges the FDA response and thanks the FDA for affirming that the Sponsor's proposed plan (to include the GLP status for all studies, deviations from GLP, and an assessment of the impact on the interpretation of the results) is acceptable, however the adequacy of the submitted studies and the need for additional studies, will be a review issue. The timing of any additional nonclinical studies would follow the Sponsor response in Q11 above.

Administrative question:

Q13 Does the Agency agree with the Sponsor's plan for submitting the defibrotide NDA (b) (4)

FDA Response:

(b) (4)

Sponsor Response/ Meeting Discussion

No discussion needed.

Additional Comments:

☐ We recommend that you explore the feasibility of additional prospective randomized clinical trials to support your application. A randomized early intervention trial is one possibility you may want to consider. We recommend that you submit a synopsis of any future protocols you may be considering.

☐ Please include the SAS programs used to derive the primary and key secondary efficacy endpoints from the SDTM data. SAS programs used for the primary and key secondary efficacy endpoints analyses based on ADaM data and for any new results included in the proposed labeling should also be included. Note that these SAS programs need to include all pivotal and supportive studies with efficacy findings.

Sponsor Response/ Meeting Discussion

No discussion needed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROMEO A DE CLARO
08/29/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 62118

MEETING MINUTES

Jazz Pharmaceuticals, Inc.
US Regulatory Agent for Gentium S.p.A.
Attention: Robin Hume, MS, RAC
Director of Regulatory Affairs
40 Worth Street, 10th Floor
New York, NY 10013

Dear Ms. Hume:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Defibrotide.

We also refer to the meeting between representatives of your firm and the FDA on August 7, 2014. The purpose of the meeting was to discuss the CMC data to be submitted in a future defibrotide NDA.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jewell Martin, Regulatory Project Manager at (301) 796- 2072.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA CMC

Meeting Date and Time: August 7, 2014; 11:00- 12:00 PM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: IND 62118
Product Name: Defibrotide.
Indication: For the treatment of (b) (4) hepatic veno-occlusive disease (VOD) following hematopoietic stem cell transplant (HSCT) therapy
Sponsor/Applicant Name: Gentium S.p.A./Jazz Pharmaceuticals, Inc.

FDA ATTENDEES
Ali Al Hakim, PhD, Branch Chief, ONDQA
Janice Brown, MS, CMC Lead, ONDQA
Vinayak Pawar, PhD, Microbiology Reviewer, OPS
Jewell Martin, MA, MBA, PMP, Regulatory Project Manager, ONDQA

SPONSOR ATTENDEES
Krishna Allamneni, DVM, PhD, DABT, Executive Director, Nonclinical Development, Jazz
William Bennett, Head of Biologics Development, Product Development, Jazz
Michael Desjardin, SVP, Manufacturing & Technical Development, Jazz
Jennifer Ekelund, VP, US Regulatory Affairs, Jazz
Robin Hume, M.S. RAC, Director, Regulatory Affairs, Jazz / US Agent for Gentium
Terenzio Ignoni, VP, Quality and Qualified Person, Gentium
Vijay Kumar, Quality Control Compliance Manager, Gentium
Charles LaPree, Global Head of Regulatory Affairs, Jazz
Catherine Lunny, Director, Global Regulatory Affairs, CMC, Jazz
(b) (4)
Joel Selcher, Ph.D., Senior Director, Regulatory Affairs, Jazz

1.0 BACKGROUND

In a letter dated May 15, 2014, Gentium S.p.A./ Jazz Pharmaceuticals, Inc. requested a Type B, Pre-NDA, Chemistry, Manufacturing, and Controls (CMC) meeting. The purpose of this meeting is to discuss the data to be submitted in a future defibrotide NDA. The Office of New Drug Quality Assessment (ONDQA) issued a Meeting Granted letter to Gentium S.p.A./ Jazz Pharmaceuticals, Inc. on June 17, 2014. Gentium S.p.A./Jazz Pharmaceuticals, Inc. submitted their meeting background package on July 9, 2014. A revised copy of the background package was submitted on July 28, 2014 which includes a referenced source table omitted from

the original background package. On August 6, 2014, Gentium S.p.A./Jazz Pharmaceuticals, Inc. requested further discussion on Questions 6, 3, 7, 1, and 2, and provided handouts to aid in meeting discussion (see attached).

2.0 DISCUSSION

Question 1:
Does the Agency agree with the Sponsor's approach to the risk assessment of viral load in the porcine intestinal mucosa material requested by FDA?

FDA Response to Question 1:
Based on the control measures (b) (4) **in place to assure quality mucosa and the manufacturing process steps providing higher level of virus clearance than the viral clearance validation studies with model viruses, provide acceptable assurance with the sponsor's approach to risk assessment of viral load. Although this preliminary risk assessment is acceptable, the Agency looks forward to receiving the Final Risk Assessment document with the NDA submission to include: (a) control measures to assure the quality of the porcine intestinal mucosa, (b) validated viral clearance of the defibrotide** (b) (4) **(c) viral load assessment** (b) (4)

Meeting Discussion:
The Agency stated that they will review the final risk assessment with the submission of Module 3.

Question 2:
Based on the information provided in this briefing document, does the Agency agree that the specific retroviral clearance study is not required to be included in the defibrotide NDA submission.

FDA Response:
Sponsor's claim that Retroviruses are only weakly resistance to physiochemical inactivation based on the conclusion that the porcine retrovirus represents no higher challenge for viral clearance than the model enveloped viruses used in the existing validation of the orthogonal viral clearance study generated by (b) (4) **in July 2014. This claim is acceptable, however, conclusion can be only drawn when the results of the viral identification study being conducted on the intestinal mucosal material are available. A need for a specific retroviral clearance study can be only determined when the Agency reviews the Final Risk Assessment document to be submitted with the NDA.**

Meeting Discussion:

The Agency stated that they will review the final risk assessment with the submission of Module 3.

Final determination of the acceptability of the characterization data will be made at the NDA review when complete CMC information is assessed.

Meeting Discussion:
The Sponsor agreed to submit additional characterization data to cover the (b) (4) The Sponsor stated that the data represent a transformation of the output of the validated software.

Question 4:
Does the Agency agree that the tests conducted are acceptable to characterize (b) (4) (b) (4) (b) (4) (b) (4) defibrotide?

FDA Response to Question 4:
Your approach to characterize (b) (4) of defibrotide appears acceptable. However, final determination of the acceptability of the characterization (b) (4) of defibrotide will be made at the NDA review when complete CMC information is assessed.

Meeting Discussion:
No further discussion required.

Question 5:
Does the Agency agree that the data provided in the briefing document are sufficient to address FDA's request to correlate the biological activity with (b) (4) (b) (4) of defibrotide?

FDA Response to Question 5:

Your approach to study the correlation between the biological activity and the [redacted] (b) (4) of defibrotide appears acceptable. Please also refer to the response to Question #3. Whether the data is sufficient to demonstrate such correlation is a review issue, and will be determined at the NDA review.

Meeting Discussion:
No further discussion required.

Question 6:
Does the Agency agree that the release specification presented in this briefing document for the defibrotide drug substance is acceptable?

FDA Response to Question 6:
[redacted] (b) (4) should be controlled at the whole range. Refer to the response to Question #3. The acceptance criterion for biological assay should be a range [redacted] (b) (4) Note that determination of the acceptability of the defibrotide drug substance specification will be made at the NDA review when complete CMC information is assessed.

Meeting Discussion:
The Sponsor agreed to include a [redacted] (b) (4) for the acceptance criteria for the biological assay. The proposal to establish an upper limit using + / - 3 SD from the mean appears acceptable; however, a final determination will be made during the review of your NDA.

The Agency stated that the proposed [redacted] (b) (4) t [redacted] (b) (4) control parameter will be a review issue.

Question 7:
Does the Agency agree that the proposed draft drug product specifications including the modifications requested by the Agency are acceptable to support the NDA?

FDA Response to Question 7:
No, you have not addressed FDA's comments to Question #11 in the December 4, 2013, preNDA meeting responses. You will need to include the following in the drug product specification:

1. **Identity test**
2. **Replace of the test for Titre with Assay is not just a name change. Instead, it is a change of analytical method.**
3. **Refer to the response to Question #6 for biological assay.**

Final determination of the acceptability of the proposed drug product specification will be made at the NDA review when complete CMC information is assessed.

Meeting Discussion:

(b) (4)

The Agency referred to the response and discussion in question 6 concerning the upper limit for the biological assay.

Question 8:
Does the Agency agree that the approach for demonstration of comparability between the defibrotide drug product used in the 2005-01 pivotal study and the defibrotide commercial drug product is acceptable?

FDA Response to Question 8:
Your approach appears to be acceptable. Final determination of the acceptability will be made at the NDA review when complete CMC information is assessed.

Meeting Discussion:
No further discussion required.

3.0 ACTION ITEMS

There are no specific due dates or time lines for submission of information or other action items. General agreements and commitments are included in the Discussion section (2.0) above.

4.0 ATTACHMENTS AND HANDOUTS

Handouts were provided by Gentium S.p.A./ Jazz Pharmaceuticals, Inc. on August 6, 2014 (see attached).

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/s/

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08/12/2014

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208114

LATE-CYCLE MEETING MINUTES

Gentium S.p.A.
c/o Jazz Pharmaceuticals, Inc.
Attention: Robin Hume, MS, RAC
Director, Regulatory Affairs, US Agent
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Hume:

Please refer to your New Drug Application (NDA) dated July 31, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Defitelio (defibrotide) injection, 200 mg/2.5 mL.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on January 26, 2016.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: January 29, 2016; 8:30 AM – 10:00 AM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1417
Silver Spring, Maryland 20903

Application Number: NDA 208114
Product Name: Defitelio (defibrotide)
Sponsor/Applicant Name: Gentium S.p.A. (a Jazz Pharmaceuticals company)

Meeting Chair: R. Angelo de Claro, MD
Meeting Recorder: Beatrice Kallungal, BS

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)
Richard Pazdur, MD, Director

OHOP/Division of Hematology Products
Ann Farrell, MD, Director
R. Angelo de Claro, MD, Clinical Team Leader
Donna Przepiorka, MD, PhD, Clinical Reviewer
Tanya Wroblewski, MD, Clinical Reviewer
Yvette Kasamon, MD, Clinical Reviewer
Theresa Carioti, MPH, Chief, Project Management Staff
Diane Leaman, BS, Safety Regulatory Project Manager
Beatrice Kallungal, BS, Senior Regulatory Project Manager

OHOP/Division of Hematology, Oncology, Toxicology
Christopher Sheth, PhD, Team Leader
Brenda Gehrke, PhD, Reviewer

Office of Biostatistics/Division of Biometrics V
Lei Nie, PhD, Team Leader
Xin Gao, PhD, Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Bahru Habtemariam, PharmD, Team Leader

Office of Pharmaceutical Quality (OPQ)/Division of New Drug Products
Anamitro Banerjee, PhD, Application Technical Lead
Janice Brown, MS, CMC Lead
Youmin Wang, PhD, Reviewer, Division of Process Assessment

OPQ/Office of Process and Facilities (OPF)/Division of Inspectional Assessment (DIA)
Quallyna Porte, Interdisciplinary Scientist

Office of Surveillance and Epidemiology (OSE)/Division of Epidemiology I (DEPI I)
Carolyn McCloskey, MD, MPH, Epidemiologist
Sarah Harris, PharmD, Safety Regulatory Project Manager

OSE/Division of Medication Error Prevention and Analysis (DMEPA)
Nicole Garrison, PharmD, BCPS, Reviewer

EASTERN RESEARCH GROUP ATTENDEE
Chris Sese, Independent Assessor

APPLICANT ATTENDEES
Charles LaPree, MS, Head of Global Regulatory Affairs
Jennifer Ekelund, Vice President, US Regulatory Affairs
Joel Selcher, PhD, Executive Director, Global Regulatory Affairs
Robin Hume, MS, RAC, Director, Regulatory Affairs, Jazz/US Agent for Gentium
Amanda Roodhouse, Manager, Regulatory Strategy
Joanne Curley, Executive Director, Global Promotional Regulatory Affairs and Labeling
William Bennett, Head of Biologics Development
(b) (4)
William Tappe, MD, Director, Clinical Development, Hematology/Oncology
Maja Miloslavsky, PhD, Senior Director, Biostatistics
Jin Zhu, PhD, Director, Biostatistics
Mark Eller, PhD, Head of Early Development and Clinical Pharmacology
Taruna Arora, PhD, Senior Director, Immunology and Nonclinical Development
Krishna Allamneni, PhD, DVM, DABT, Executive Director, Nonclinical Development
John Miller, Global Product Team Leader, Hematology/Oncology
Eileen Connolly, Associate Director, Global Regulatory Affairs, CMC
Terenzio Ignoni, Vice President, Quality and Qualified Person
Tim Corn, MD, Development Team Leader, Hematology/Oncology
Kamalika Banerjee, Senior Manager, Biostatistics

1.0 BACKGROUND

NDA 208114 was submitted on July 31, 2015 for Defitelio (defibrotide).

Proposed indication: For the treatment of hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with (b) (4) dysfunction following hematopoietic stem-cell transplantation (HSCT).

PDUFA goal date: March 31, 2016

FDA issued a Background Package in preparation for this meeting on January 13, 2016.

2.0 DISCUSSION

LCM AGENDA

I. Introductory Comments – 5 minutes (RPM/CDTL)
Welcome, Introductions, Ground rules, Objectives of the meeting

II. Discussion of Substantive Review Issues and Postmarketing Requirements/Postmarketing Commitments– 20 minutes

Meeting Discussion:

No discussion.

III. Major labeling issues – 20 minutes

Clinical and Statistics

1. (b) (4)

2. Because the significance level adjusting for the many unplanned adaptations and multiple analyses was not pre-specified, the nominal p-values obtained from the analyses are not interpretable.

Meeting Discussion:

The Agency and the Applicant acknowledged the challenges of analyzing and interpreting the results from a historical controlled trial. The Applicant provided clarification on their revised proposal which the Agency will review further during labeling negotiations.

3. (b) (4)

Meeting Discussion:

The Agency will review the Applicant's proposal (b) (4)

4. [redacted] (b) (4)

Meeting Discussion:

The Agency provided feedback regarding the Applicant's revision to section 2.1 of the United States Prescribing Information (USPI).

5. The proposed indication was changed [redacted] (b) (4) (b) (4)

Meeting Discussion:

The Agency provided feedback regarding Applicant's revisions to section 6 of the USPI.

Product Quality and Clinical Pharmacology

1. The USP <1121> Salt Policy stipulates that USP will base the strength of the drug product on the active moiety. Sections 3, 11 and 16 of the full prescribing information have been revised to include the following equivalency statement to indicate the amount of active moiety present: [redacted] (b) (4) 80 mg of defibrotide sodium salt. Revise the strength in the immediate container label and carton and include the strength [redacted] (b) (4)

There are exceptions to the USP <1121> Salt Policy. CDER has determined that the name of the salt should be retained if any of the following is true:

a. The active ingredient is a relatively simple salt and administration of the entire salt is therapeutically important. Examples include lithium carbonate; iron sulfate, and other oral and intravenous iron salts; calcium gluconate and other calcium salts; potassium chloride; magnesium sulfate; sodium or potassium phosphate; and sodium citrate.

b. Scientific evidence demonstrates the salt form affects the absorption, distribution, metabolism, and/or excretion (ADME) of the drug in a manner that influences the clinician's product selection.

c. Clinically significant amounts of cations such as sodium, potassium, magnesium or calcium accompany the active moiety of a drug product. Clinical significance may be related to the recommended maximum daily amount of an electrolyte intake in special patient populations. Examples would include recommended daily intake of sodium in patients with congestive heart failure or recommended daily intake of potassium in patients with chronic kidney disease.

d. There is significant evidence-based safety concern that the counter-ion part of the salt could cause acid-base disturbances, hepatic, renal or other organ damage, or hypersensitivity reactions.

(b) (4)

(b) (4)

6.25 mg/kg dose of defibrotide sodium salt.

Regarding the nomenclature of your product, the International Nonproprietary Name (INN) lists your drug product as the active moiety, defibrotide, not defibrotide, sodium salt. We agree that in section 11 of the full prescribing information that the drug substance is defibrotide, sodium salt that the chemical name should remain as polydeoxyribonucleotide, sodium salt, (b) (4) 80 mg of defibrotide, sodium salt).

Meeting Discussion:

The Agency acknowledged the Applicant's response submitted on January 22, 2016. At the Late Cycle Meeting, the Agency identified two possible options for the Applicant. The first option would be to use a United States Adopted Names (USAN) of defibrotide sodium. This will allow the Applicant to keep the proposed dosing of 6.25 mg/kg and strength of 80 mg/mL. (b) (4) ***The Applicant agreed to change USAN to defibrotide sodium and to keep the existing USAN definition.***

The Agency is committed to providing the Applicant a determination of whether this would affect the approvability of the NDA, within one week. The Agency was also informed of the discrepancies with the INN. The Applicant will update the NDA with the current INN, accordingly.

2. In the PI, the statement "administer the diluted Defitelio solution using an infusion set equipped with a 0.2 micron in-line filter" is not supported by a compatibility study for the diluted product using an in-line filter. Either provide compatibility data of the diluted product sampled after the in-line filter or remove the use of the in-line filter in the PI.

Meeting Discussion:

The Applicant committed to perform the in-use stability study using in-line filter and submit the results of the study to the NDA within two weeks.

IV. Review Plans – 5 minutes
The user fee goal date is March 31, 2016.

V. Wrap-up and Action Items – 5 minutes

- ***The Applicant committed to submit revised USPI by February 5, 2016.***
- ***The Applicant committed to perform the in-use stability study using in-line filter and submit the results of the study to the NDA within two weeks.***
- ***The Agency committed to provide the Applicant a determination of whether issues with USAN nomenclature would affect the approvability of the NDA, within one week.***

This application has not yet been fully reviewed by the signatory authority, division director, Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

Post meeting comment:
The lack of an official USAN will not affect the approvability of your NDA. We acknowledge your commitment to request a USAN of defibrotide sodium.

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/s/

ROMEO A DE CLARO
02/05/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208114

LATE CYCLE MEETING
BACKGROUND PACKAGE

Gentium S.p.A.
c/o Jazz Pharmaceuticals, Inc.
Attention: Robin Hume, MS, RAC
Director, Regulatory Affairs, US Agent
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Hume:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Defibrotide solution for infusion, 200 mg/2.5mL.

We also refer to the Late-Cycle Meeting (LCM) scheduled for January 26, 2016. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	January 26, 2016; 10:00 AM – 11:00 AM EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1421 Silver Spring, Maryland 20903
Application Number:	NDA 208114
Product Name:	Defibrotide
Indication:	For the treatment of hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with (b) (4) dysfunction following hematopoietic stem-cell transplantation (HSCT)
Sponsor/Applicant Name:	Gentium S.p.A. (a Jazz Pharmaceuticals company)

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

1. DISPLINE REVIEW LETTERS

No Discipline Review letters have been issued to date.

2. SUBSTANTIVE REVIEW ISSUES

The following substantive review issues have been identified to date:

Clinical

1. The instructions for adverse event recording in the pivotal trial and the supporting studies excepted many events. As such, the safety profile for defibrotide in your proposed prescribing information (PI) may be incomplete. In order to confirm the verity of the proposed safety profile, you will need to submit safety results from a trial of defibrotide which required reporting of all adverse events.

2. The assessment of vital signs in the pivotal trial and the supporting studies was limited to daily measurement. This is not sufficient to objectively exclude the occurrence of infusion reactions. You will need to submit frequent measurements of vital signs during and immediately after infusion of defibrotide in a clinical study in order to assess objectively the incidence of infusion reactions.

3. You have provided no measurements of anti-drug antibodies in subjects treated with defibrotide.

In order to address the above issues we require you to complete the following postmarketing requirements/commitments

- Conduct an analysis of safety in a randomized, open-label multi-center clinical trial comparing defibrotide versus best supportive care in the prevention of hepatic VOD in adult and pediatric patients, including all adverse events, laboratory abnormalities and frequent peri-infusion vital signs.

- Develop sensitive and specific anti-drug (defibrotide) binding and neutralizing assays. Submit validation reports on the assays in a final report to the NDA.

- Evaluate patients' sera for binding and neutralizing antibodies to defibrotide using the validated assays from PMC 1 and submit the data in a final immunogenicity study report.

Statistics

FDA has the following major concerns (b) (4)

(b) (4)

3. ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

4. REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

5. CLINICAL AND MANUFACTURING SITE INSPECTIONS

The final inspection reports for clinical and manufacturing sites are still pending.

LCM AGENDA

I. Introductory Comments – 5 minutes (RPM/CDTL)
Welcome, Introductions, Ground rules, Objectives of the meeting

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III. Major labeling issues – 20 minutes

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(b) (4)

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There are exceptions to the USP <1121> Salt Policy. CDER has determined that the name of the salt should be retained if any of the following is true:

a. The active ingredient is a relatively simple salt and administration of the entire salt is therapeutically important. Examples include lithium carbonate; iron sulfate, and other oral and intravenous iron salts; calcium gluconate and other calcium salts; potassium chloride; magnesium sulfate; sodium or potassium phosphate; and sodium citrate.

b. Scientific evidence demonstrates the salt form affects the absorption, distribution, metabolism, and/or excretion (ADME) of the drug in a manner that influences the clinician's product selection.

c. Clinically significant amounts of cations such as sodium, potassium, magnesium or calcium accompany the active moiety of a drug product. Clinical significance may be related to the recommended maximum daily amount of an electrolyte intake in special patient populations. Examples would include recommended daily intake of sodium in patients with congestive heart failure or recommended daily intake of potassium in patients with chronic kidney disease.

d. There is significant evidence-based safety concern that the counter-ion part of the salt could cause acid-base disturbances, hepatic, renal or other organ damage, or hypersensitivity reactions.

(b) (4)

(b) (4)
6.25 mg/kg dose of defibrotide sodium salt.

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80 mg of defibrotide, sodium salt).

2. In the PI, the statement "administer the diluted Defitelio solution using an infusion set equipped with a 0.2 micron in-line filter" is not supported by a compatibility study for the diluted product using an in-line filter. Either provide compatibility data of the diluted product sampled after the in-line filter or remove the use of the in-line filter in the PI.

IV. Review Plans – 5 minutes
The user fee goal date is March 31, 2016.

V. Wrap-up and Action Items – 5 minutes

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/s/

ROMEO A DE CLARO
01/13/2016