

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207793Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: October 21, 2015
Requesting Office or Division: Division of Oncology Products 2 (DOP2)
Application Type and Number: NDA 207793
Product Name and Strength: Onivyde (irinotecan liposome injection),
43 mg/10 mL (4.3 mg/mL)
Submission Date: October 16, 2015 and October 20, 2015
Applicant/Sponsor Name: Merrimack Pharmaceuticals, Inc.
OSE RCM #: 2015-473-2
DMEPA Primary Reviewer: Otto L. Townsend, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Oncology Products 2 (DOP2) requested that we review the revised container label and carton labeling for Onivyde (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

Upon review of the revised container label we determined that it required an additional modification. To address this issue, the following recommendation was conveyed to the Applicant via electronic mail on October 19, 2015:

The concentration statement should have a space between the numeral (4.3) and the unit (mg). Please change the concentration per mL statement to include a space. For example: change 4.3mg/mL to 4.3 mg/mL.

¹ Townsend O. Label and Labeling Review Memorandum for Onivyde (NDA 207793). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 OCT 13. 3 p. OSE RCM No.: 2015-473-1.

The Applicant made the recommended change and submitted the updated container label on October 20, 2015 (Appendix A).

2 CONCLUSION

The revised container label and carton labeling for Onivyde is acceptable from a medication error perspective. We have no further recommendations at this time.

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

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/s/

OTTO L TOWNSEND
10/21/2015

CHI-MING TU
10/21/2015

505(b)(2) ASSESSMENT

Application Information		
NDA # 207793	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Onivyde Established/Proper Name: irinotecan liposome injection Dosage Form: Injection Strengths: 50 mg/10 mL		
Applicant: Merrimack Pharmaceuticals, Inc.		
Date of Receipt: April 24, 2015		
PDUFA Goal Date: October 24, 2015	Action Goal Date (if different): October 23, 2015	
RPM: Deanne Varney		
Proposed Indication: Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
<i>Camptosar (irinotecan hydrochloride injection) NDA 20571</i>	<i>FDA's previous finding of safety and effectiveness (clinical and nonclinical)</i>

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

This efficacy supplement relies on FDA's prior findings of safety and effectiveness for the listed drug, Camptostar. A BA/BE study was not required because the PK profile of the liposomal formulation is expected to be different than the non-liposomal formulation.. The ability to rely on these prior findings is based on the same active pharmaceutical ingredient (irinotecan hydrochloride) in both Camptostar and Onivyde. The only effect of the liposome has is to change the kinetics of irinotecan by modifying e.g., slowing, the release of irinotecan from the liposome. The sponsor provided in-vitro and in-vivo data showing that irinotecan is released from the liposome. In addition, animal studies indicated that the toxicity profiles of Onivyde and Camptosar are comparable.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO

If "NO," proceed to question #5.

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Camptosar	20571	Y (per 356h)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If “**YES**”, please list which drug(s) and answer question d) i. below.

If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

- This application provides for a new indication: Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine.
- This application also provides for a new formulation (liposomal).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

*If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"

If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): Camptosar

PATENT CERTIFICATION/STATEMENTS
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12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

6403569 - 4/28/2020 (U-449)

6403569*PED - 10/28/2020

6794370 – 5/1/2020 (U-606)

6794370*PED – 11/1/2020

No patents listed proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If “**NO**”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent numbers / Method of Use Codes:

6403569 - U-449: USE IN COMBINATION WITH 5-FLUOROURACIL AND LEUCOVORIN FOR THE TREATMENT OF METASTATIC COLORECTAL CANCER WHERE THE DOSE OF LEUCOVORIN IS AT LEAST 200MG PER SQUARE METER

6794370 – U-606: USE OF IRINOTECAN IN COMBINATION WITH 5-FLUOROURACIL AND LEUCOVORIN FOR THE TREATMENT OF METASTATIC COLRECTAL CANCER

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

DEANNE R VARNEY
10/20/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: October 13, 2015
Requesting Office or Division: Division of Oncology Products 2 (DOP2)
Application Type and Number: NDA 207793
Product Name and Strength: Onivyde (irinotecan liposome injection),
43 mg/10 mL (4.3 mg/mL)
Submission Date: October 8, 2015
Applicant/Sponsor Name: Merrimack Pharmaceuticals, Inc.
OSE RCM #: 2015-473-1
DMEPA Primary Reviewer: Otto L. Townsend, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Oncology Products 2 (DOP2) requested that we review the revised container label and carton labeling for Onivyde (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective because the proprietary and established names are not the most prominent information on the principal display panels and critical product information has been moved to the side panel of the container label.

¹ Townsend O. Label and Labeling Review for Onivyde (NDA 207793). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JUL 27. 8 p. OSE RCM No.: 2015-473.

3 RECOMMENDATIONS FOR MERRIMACK

We recommend the following be implemented prior to approval of this NDA:

A. Container Label

1. The Principal Display Panel (PDP), as currently presented, appears crowded without adequate white space. Additionally, the (b) (4) is not essential information to promote the safe use of this drug product that crowds the PDP and still competes in prominence with proprietary and established names.
 - i. Per 21 CFR 201.10(g)(2), ensure that the established name is at least one-half the height of the proprietary name.
 - ii. Delete (b) (4).
2. Unbold the font used for the National Drug Code (NDC) and “Rx Only” statement.
3. Relocate the “(b) (4)” and “(b) (4)” statements from the side panel to the PDP and revise to read “For Intravenous Infusion After Dilution”.
4. Change the strength statement so that the total product strength per total volume is bolded. For example:

43 mg/10 mL
(4.3 mg/mL)

Please note the strength, 43 mg/10 mL, is bolded; and the concentration, 4.3 mg/mL, is not bolded.

5. Unbold the statement, “Store ONIVYDE™ in original carton to protect from light.”

B. Carton Labeling

1. See Comment A.4.
2. On the PDP and back panel, revise the “(b) (4)” and “(b) (4)” statements to read “For Intravenous Infusion After Dilution” and relocate it so that it is immediately below the product strength statement (see example below):

43 mg/10 mL
(4.3 mg/mL)

For Intravenous Infusion After Dilution

2 1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

OTTO L TOWNSEND
10/13/2015

CHI-MING TU
10/13/2015

Internal Consult

****Pre-decisional Agency Information****

To: Deanne Varney, Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology Oncology Products

From: Carole C. Broadnax, R.Ph., Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Date: October 13, 2015

Re: **ONIVYDE (irinotecan liposome injection) tablets, for intravenous use**
NDA 207793
Addendum to OPDP Comments on proposed draft product labeling (Package Insert)

In response to the Division of Oncology Products 2 (DOP 2)'s May 4, 2015, consult request, OPDP provided initial comments on October 8, 2015, for proposed product labeling (Package Insert (PI)) for ONIVYDE (irinotecan liposome injection) tablets, for intravenous use.

This addendum is for OPDP's two additional comments in the Highlights section of the proposed PI (attached) that were conveyed to DOP-2 via SharePoint on October 9, 2015.

The version of the proposed PI used in this review was sent to OPDP (Carole Broadnax) from DOP-2 (Deanne Varney) via a link to Share Point contained in electronic mail dated October 8, 2015, and is titled, "20151008_MM-398 USPI Tracked_FDA Edits.docx."

Thank you for your consult. If you have any questions, please contact Carole Broadnax at 301-796-0575 or Carole.Broadnax@fda.hhs.gov.

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/s/

CAROLE C BROADNAX
10/13/2015

Internal Consult

****Pre-decisional Agency Information****

To: Deanne Varney, Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology Oncology Products

From: Carole C. Broadnax, R.Ph., Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Date: October 8, 2015

Re: **ONIVYDE (irinotecan liposome injection) tablets, for intravenous use**
NDA 207793
Comments on proposed product labeling (Package Insert and carton/container)

In response to the Division of Oncology Products 2 (DOP 2)'s May 4, 2015, consult request, OPDP has reviewed proposed product labeling (Package Insert (PI) and carton/container) for ONIVYDE (irinotecan liposome injection) tablets, for intravenous use. The version of the substantially complete PI used in this review was sent via electronic mail from DOP-2 on October 2, 2015, and is titled, "20151002_USPI clean NDA 207793_FDA Edits.docx." The version of the carton and container labeling used in this review was sent via electronic mail from DOP 2 on October 7, 2015.

OPDP's comments for the PI are provided directly in the attached PDF document. Please note that for the PI, OPDP removed deletions and accepted formatting changes so that OPDP comments are easier to read.

OPDP does not have any comments on the carton and container labeling at this time.

Thank you for your consult. If you have any questions, please contact Carole Broadnax at 301-796-0575 or Carole.Broadnax@fda.hhs.gov.

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/s/

CAROLE C BROADNAX
10/08/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: October 2, 2015

TO: Deanne Varney, Regulatory Project Manager
Shan Pradhan, M.D., Medical Reviewer
Division of Oncology Products 2

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 207793

APPLICANT: Merrimack Pharmaceuticals, Inc.

DRUG: Onivyde™ (Irinotecan Liposome Injection)

NME: No

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: For the treatment of patients with metastatic adenocarcinoma of the pancreas.

CONSULTATION REQUEST DATE: May 11, 2015
INSPECTION SUMMARY GOAL DATE: September 30, 2015
DIVISION ACTION GOAL DATE: October 24, 2015
PDUFA DATE: October 25, 2015

I. BACKGROUND:

This 505 (b) (2) NDA seeks marketing approval of Irinotecan Liposome Injection. The product is a 10 mL single-use vial containing 5 mg/mL of irinotecan hydrochloride trihydrate solution to deliver a dose of 50 mg for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine.

The application is supported by safety and efficacy results of one Phase 3 Study, MM-398-07-03-01, "NAPOLI-1: A Randomized, Open Label Phase 3 Study of MM-398, with or without 5-Fluorouracil and Leucovorin, versus 5-Fluorouracil and Leucovorin, in Patients with Metastatic Pancreatic Cancer Who have Failed Prior Gemcitabine-based Therapy."

The study was originally designed with two treatment arms, comparing MM-398 monotherapy with a control of 5-FU/LV; subjects were randomized in a 1:1 ratio to the treatment arms. The study was amended to add a third arm to investigate the combination treatment of MM-398 with 5 FU/LV (MM-398+5FU/LV) and expanded to enroll approximately 405 patients. At the time the amendment was instituted, 63 patients had been randomized under the original two arm protocol. Study MM-398-07-03-01 randomized 417 subjects at 76 clinical centers worldwide. The clinical development for this formulation is covered in IND 102779.

The primary endpoint was overall survival (OS). Secondary efficacy endpoints were investigator-assessed tumor response per RECIST v1.1 criteria; progression free survival (PFS), time to treatment failure (TTF) and objective response rate (ORR).

Five clinical sites were chosen for inspection: These sites were selected for inspection using CDER's Clinical Site Selection Tool (CSST). The CSST uses site specific data (e.g., enrollment, AE reporting, protocol violations, inspectional history, etc.) in a multi-attribute risk prioritization algorithm to display site level data for review, and use by the application review team to select clinical investigator sites for inspection.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#1: Bodoky, Gyorgy Gyali ut 5-7 Budapest, 1097 Hungary	Protocol: MM-398-07-03-01 Site Number: 366 Number of Subjects: 23	July 3-10, 2015	Pending Interim classification: VAI
CI#2: Chen, Li-Tzong 2F No.367, Sheng Li Road Tainan, 704 Taiwan	Protocol: MM-398-07-03-01 Site Number: 881 Number of Subjects: 35	July 27-31, 2015	Pending Interim classification: NAI
CI#3: Dean, Andrew 12 Salvado Road Subiaco, Western Australia 6088, Australia	Protocol: MM-398-07-03-01 Site Number: 617 Number of Subjects: 18	August 3-6, 2015	Pending Interim classification: NAI
CI#4: Jameson, Gayle 10510 North 92nd Street Scottsdale, AZ 85258	Protocol: MM-398-07-03-01 Site Number: 120 Number of Subjects: 14	June 25-July 1, 2015	Pending Interim classification: NAI
CI#5: Li, Chung-Pin No. 201 Sec. 2 Shih-Pai Rd. Taipei, 112 Taiwan	Protocol: MM-398-07-03-01 Site Number: 882 Number of Subjects: 31	July 20-24, 2015	Pending Interim classification: NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. CI#1: Dr. Gyorgy Bodoky (Site 366)

- a. What was inspected:** The site screened twenty nine subjects, and twenty three subjects were enrolled. At the time of this inspection one subject was on treatment, seventeen subjects had terminated treatment due to disease progression per RECIST or clinical deterioration, one had an AE of multiple WBC events after a year of treatment, and four subjects had withdrawn consent/made the decision to end early in the treatment phase. Subject status is as follows; nineteen are deceased, two known alive (the 1 still participating and the one with the WBC AE), while the other two are unknown/lost to follow-up. All but one of the nineteen death events occurred prior to the February 14, 2014 data lock, and one subject died in (b) (6) after the data cut-off date. Informed consent forms were reviewed for all subjects. The subject

disposition/overall summary (study treatment end/termination reason, date of death, 1st study treatment dose) and major deviations were reviewed for all enrolled subjects. Seven subjects that received the investigational product in Arm A, as well as another three subjects in Arm B and three subjects in Arm C, had study source documents compared to eCRFs and data listings submitted to NDA 207793, focusing on inclusion/exclusion criteria compliance, adverse events, treatment regimens, reporting of AEs in accordance with the protocol, efficacy endpoint verification, and general protocol compliance. The FDA investigator also assessed test article accountability, monitoring reports, and IRB/EC correspondence.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. The primary efficacy endpoint (OS) were verified. There was no evidence of underreporting of adverse events. There were a number of minor protocol deviations at this site that appeared to be fully reported in the data listings. Examples include study visits occurring outside of the study-specified visit windows and occasional missed laboratory tests. Noteworthy, was a dosing error issue that appears to be due to confusion in the protocol related to Leucovorin being administered at 200 mg/m², whereas it should have been 400 mg/m² because the site was using the l + d racemic form. The Protocol, Section 7.3.3. Doses and Administration of 5-FU and Leucovorin, specifies that "Leucovorin will be administered at a dose of 400 mg/m² of the l + d racemic form, or l form 200 mg/m², as an IV infusion over 30 minutes, every 2 weeks. This affected eight subjects at this site and was included in the Critical Site Deviation data listing submitted to NDA 207793.

CSR Key Protocol Deviations Datalisting 16.2.1.5.1 (page 8 of 19) included the mis-dosing of eight out of nine Arm C (MM-398+5-FU/LV) randomized Subjects: Subject 366-0129, Subject 366-0133, Subject 366-0221, Subject 366-0286, Subject 366-0290, Subject 366-0350, Subject 366-0393 and Subject 366-0394 Leucovorin (l+d racem mixture) was administered at a dose of 200 mg/m² instead of 400 mg/m² at all cycles.

A Form FDA 483 was issued citing one inspectional observation.

Observation 1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

- A. There were two subjects (#366-0076 and #366-0288) who were enrolled in this study with a Vater Papilla tumor which was in violation of protocol Inclusion Criteria #1.

- B. This site used a 500 ml solution called "Rindex" that contains dextrose plus electrolytes [as the diluent for infusion of the MM-398 IP/test article in Study arms A and C] that was different from the D5W (5% Dextrose in Water) Solution specified in the protocol. This practice extended from the beginning of the study in July of 2012 until the solution was changed in June of 2013, after being identified by a study monitor.

OSI Notes: With respect to item 1.A., Dr. Bodoky concurred with the inspectional observation in his written response to the Form FDA 483, dated July 24, 2015. Dr. Bodoky informed that the entry criteria violations for Subjects #366-0076 and #366-0288 was identified by the clinical monitor on June 20, 2013. The monitor/CRA immediately conducted site staff re-training on June 21, 2013. Evidence of a site training log was provided in the written response, dated July 24, 2015, from Dr. Bodoky. The site had no additional protocol deviations regarding subject eligibility subsequent to the training. Both protocol violations were also reported to the Ethics Committee in accordance with local regulations. Dr. Bodoky also informed that the sponsor determined that these subjects were to be excluded from the study analysis. These protocol deviations are reported in the NDA 207793, CSR, Appendix 16.2.2 Protocol Deviations, Listing 16.2.1.5.1 Key Protocol Deviations. The review division may wish to confirm whether these subjects were in fact excluded from all study outcome analysis, and include or exclude as appropriate. However, these subjects represent a small proportion of study subjects in this study and their data should not importantly impact overall study outcome. Finally, there is no evidence to suggest that the inclusion of these two subjects into Study MM-398-07-03-01 resulted in harm.

Subject #366-0076 was randomized to the test article IP monotherapy arm, MM-398. As reported in NDA 207793 data listings, this subject experienced no treatment-related SAEs while on study. The last dose of study drug for this subject was administered on March 3, 2013. The subject was found to have disease progression on April 3, 2013, after 9 treatment cycles. Treatment for Subject #336-0076 was stopped due to disease progression.

Subject #366-0288 was randomized to the active comparator Arm (leucovorin + 5FU). After discovery of the entry criteria violation for this subject, the monitor/CRA sent an email to Dr. Bodoky on June 24, 2013 stating that this subject could stay in the study until disease progression. Subsequently, this subject received two cycles of treatment. On August 13, 2013 a CT scan showed disease progression. The subject had SAEs of grade 3 vomiting and GI obstruction deemed not to be treatment-related, from July 2-4, 2014. The subject died on [REDACTED] (b) (6)

With respect to item 1.B., Dr. Bodoky concurred with the observation in a written response to the Form FDA 483, dated July 24, 2015. Dr. Bodoky stated that in Hungary, the routine clinical practice is to use RINDEX solution when a treatment calls for the use of a glucose-based solution for dilution. RINDEX was used at this site until June 27, 2013, when the clinical monitor discovered the protocol deviation. Subsequently, the site staff immediately began using 5% Dextrose [D5W] as the diluent

for preparing MM-398 moving forward. Dr. Bodoky also provided documentation of retraining of the site staff that occurred on June 27, 2013.

During the current FDA inspection Dr. Bodoky communicated the use of RINDEX at their study site to the study sponsor [Merrimack] via email on July 8, 2015. A copy of the email notification was included in the written response to the Form FDA 483. Merrimack responded in writing, memorandum dated July 8, 2015, stating that subjects who had received RINDEX on either MM-398-containing treatment arms (A or C), a total of fifteen subjects, had data analyzed and compared with the remainder of the study population with respect to AEs, Disposition and Efficacy (OS). Merrimack stated that there appeared to be no impact on these subjects with respect to safety and efficacy. These subjects represent a small proportion of study subjects in this study and their data should not importantly impact overall study outcome.

Regarding the leucovorin dosing errors found for eight of nine subjects randomized to Arm C at this site, these subjects represent 8 of 117 (7%) subjects in the ITT population randomized to Arm C for the study population. In addition, based upon the datalistsings submitted to the application Subjects 366-0129, 366-0286, 366-0393 and 366-0393 were excluded from study analyses; due to insufficient dosing (Per-Protocol reason for exclusion). Therefore, while it is unclear why the remaining 4 Subjects' data were not excluded from study analysis datasets, the small number of affected subjects' who were under dosed with leucovorin should not importantly impact overall study outcome. These observations were also discussed with DOP2 Clinical Reviewer Shan Pradhan and CDTL Steven Lemery on October 2, 2015. They stated that it is unclear what if any effect the misdosing of leucovorin on those eight subjects enrolled at Site 366 had on the efficacy outcomes of these subjects, due to limited data regarding the effectiveness of these drugs in this clinical setting. However, it is unlikely that the decreased leucovorin doses would have caused increased toxicity.

- c. Assessment of data integrity:** The data for Dr. Gyorgy Bodoky' site, associated with Study MM-398-07-03-01 submitted to the Agency in support of NDA 207793, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. CI#2: Dr. Li-Tzong Chen (Site 881)

- a. What was inspected:** The site screened forty four subjects and thirty five subjects were enrolled. The study records of all enrolled subjects were audited. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 207793, focusing on inclusion/exclusion criteria compliance, adverse events, treatment regimens, reporting of AEs in accordance with the protocol, efficacy endpoint verification, and general protocol

compliance. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Records and procedures were clear, and generally well organized. The primary efficacy endpoint of OS was verifiable for all subjects. Review of source documentation for eligibility, treatment regimens and drug accountability found no major discrepancies. The inspection found that there was a leucovorin shortage during the conduct of the study at this site. Three Subjects, #881-0034, #881-0223 and #881-0224 did not receive leucovorin at one or more study visits.

Subject #881-0034 was randomized to the control Arm B, 5-FU/LV. Subject #881-0034 skipped study treatments at C6D8 on February 21, 2013 and C6D15 on Feb 27, 2013 due to the leucovorin shortage. Subject #881-0034 was only treated with 5-FU at C6D22 on March 6, 2013. According to the data submitted to NDA 207793, Subject #881-0034 missed 3 out of a total possible leucovorin treatments of 26.

Subject #881-0223 was randomized to the control Arm B, 5-FU/LV. Subject #881-0223 skipped one study treatment at C1D22 on February 21, 2013, due to the leucovorin shortage. Subject #881-0223 missed 1 out of a total possible leucovorin treatments of 28.

Subject #881-0224 was randomized to the control Arm B, 5-FU/LV. Subject #881-0224 skipped one study treatment at C1D22 on February 21, 2013, due to the leucovorin shortage. Subject #881-0224 missed 1 out of a total possible leucovorin treatments of 4.

OSI Notes: A detailed review of the application datalistings found that this site randomized 15 subjects to ARM B; thus, 3 of 15 (20%) subjects were affected by the drug shortage. In addition, 2 Subjects randomized at this site to Arm C (MM-398 + 5-FU/LV) out of 9 (20%) also had missed one leucovorin study treatment due to the drug shortage. Therefore, subjects and total missed doses of leucovorin treatments between study Arms B and C were of similar proportion and did not produce a bias between these Arms. The data produced by this site should not be substantially affected by the leucovorin missed doses. It is unlikely that these incidents significantly impacted the overall efficacy results observed in the trial. DOP2 Clinical Reviewer, Dr. Shan Pradham, informed on October 2, 2015 that it is unlikely that excluding the subjects in question would have importantly affected the overall study results.

According to the FDA field investigator, all missed leucovorin treatments were properly reported in the CSR Key Protocol Deviation data listings for this site. There were a few minor issues discussed with the site. Specifically, there were minor observations where AEs documented in the subjects' medical records were not reported to the sponsor. Also, there was a minor discrepancy found in

the data listings for secondary endpoint measures (VAS pain assessment for Subject 0513 at study week 11) when compared to the subject's source documents. These are minor inspectional observations and should not importantly impact study outcome. A Form FDA 483 was not issued.

- c. **Assessment of data integrity:** The data for Dr. Chen's site, associated with Study MM-398-07-03-01 submitted to the Agency in support of NDA 207793, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

3. CI#3: Dr. Andrew Dean (Site 617)

- a. **What was inspected:** The site screened twenty eight subjects and eighteen subjects were enrolled. The study records of all enrolled subjects were audited. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 207793, focusing on inclusion/exclusion criteria compliance, adverse events, treatment regimens, reporting of AEs in accordance with the protocol, efficacy endpoint verification, and general protocol compliance. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports.

- b. **General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Records and procedures were clear, and generally well organized. The primary efficacy endpoint of OS was verifiable for all subjects. Review of source documentation for eligibility, treatment regimens, and drug accountability found no major discrepancies. There were a few minor issues discussed with the site. There was a minor observation of a subject's weight loss which was not reported as an AE. A Form FDA 483 was not issued.

- c. **Assessment of data integrity:** The data for Dr. Dean's site, associated with Study MM-398-07-03-01 submitted to the Agency in support of NDA 207793, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

4. CI#4: Dr. Gayle Jameson (Site 120)

- a. **What was inspected:** The site screened seventeen subjects and fourteen subjects were enrolled. The study records of all enrolled subjects were audited. The record audit included comparison of source documentation to CRFs and

data listings submitted to NDA 207793, focusing on inclusion/exclusion criteria compliance, adverse events, treatment regimens, reporting of AEs in accordance with the protocol, efficacy endpoint verification, and general protocol compliance. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be good. Records and procedures were clear, and generally well organized. The primary efficacy endpoint of OS was verifiable for all subjects. There was no evidence of underreporting AEs. Review of source documentation for eligibility, treatment regimens and drug accountability found no major discrepancies. A Form FDA 483 was not issued.
- c. Assessment of data integrity:** The data for Dr. Jameson's site, associated with Study MM-398-07-03-01 submitted to the Agency in support of NDA 207793, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

5. CI#5: Dr. Chung-Pin Li (Site 882)

- a. What was inspected:** The site screened thirty nine subjects and thirty one subjects were enrolled. The study records of all enrolled subjects were audited. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 207793, focusing on inclusion/exclusion criteria compliance, adverse events, treatment regimens, reporting of AEs in accordance with the protocol, efficacy endpoint verification, and general protocol compliance. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Records and procedures were clear, and generally well organized. The primary efficacy endpoint of OS was verifiable for all subjects. Review of source documentation for eligibility, treatment regimens and drug accountability found no major discrepancies. There were a few minor issues discussed with the site: underreporting of a single instance of AE and minor date discrepancies in the data listings as compared to the site source documentation. The inspection found that there was a leucovorin shortage during the conduct of the study at this site, so some subjects did not receive leucovorin during some of their study visits.

Three Subjects, #882-0200, #882-0203 and #882-0251 did not receive leucovorin at one or more study visits.

Subject #882-0200 was randomized to the control Arm B, 5-FU/LV. Subject #882-0200 did not receive leucovorin at C2D1 on March 6, 2013, but did receive 5-FU. Subject #882-0200 missed 1 out of a total possible leucovorin treatments of 8.

Subject #882-0203 was randomized to the Active IP Arm C, MM-398 + 5-FU/LV. Subject #882-0203 did not receive leucovorin at C4D1 on March 6, 2013, but did receive 5-FU. Subject #882-0203 missed 1 out of a total possible leucovorin treatments of 5.

Subject #882-0251 was randomized to the Active IP Arm C, MM-398 + 5-FU/LV. Subject #882-0251 did not receive leucovorin at C1D1 on March 6, 2013, but did receive 5-FU. Subject #882-0251 missed 1 out of a total possible leucovorin treatments of 2.

According to the FDA field investigator, all missed leucovorin treatments were properly reported in the CSR Key Protocol Deviation data listings for this site. A Form FDA 483 was not issued.

OSI Notes: Regarding the observation related to underreporting AEs, according to the FDA field investigator, there was only one instance observed. Subject 882-0038 had reported diarrhea on August 23, 2012. This was recorded in the subject's medical records but not the datalistings submitted to NDA 207793. This event was not considered to be serious but Dr. Li agreed that this should have been reported as an AE. Subject 882-0162, had a body weight of 54kg at the start of the study and on August 23, 2013, the Subject's body weight was reported as 50.1kg. Body weight loss was not listed on the subjects AE log or the data listings. Further, on August 23, 2013, body weight loss and weakness were both reported in a review summary. Dr. Li agreed that "grade 1" weight loss is defined as weight loss over 5%, and stated it should have been reported as an AE.

A detailed review of the application datalistings found that this site randomized 11 subjects to ARM B; thus, 1 of 11 (10%) subjects were affected by the leucovorin drug shortage. This site randomized 10 subjects to Arm C (MM-398 + 5-FU/LV); thus 2 of 10 (20%) also had missed one leucovorin study treatment due to the drug shortage. Therefore, subjects and total missed doses of leucovorin treatments between study Arms B and C were of similar proportion and should not result in a substantial bias between these Arms. The data produced by this site should not be importantly affected by the leucovorin dosing errors. DOP2 Clinical Reviewer, Dr. Shan Pradham, informed on October 2, 2015 that it is unlikely that excluding the subjects in question would have importantly affected the overall study results.

- c. **Assessment of data integrity:** The data for Dr. Li's site, associated with Study MM-398-07-03-01 submitted to the Agency in support of NDA 207793, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Per the protocol, the primary efficacy endpoint was overall survival. The primary efficacy outcome measures reported in the application were verified with the source records generated at the sites. There were no trends in underreporting of adverse events.

With respect to Site 366, Dr. Gyorgy Bodoky, the inspection found that two subjects (366-0076 and 366-0288) were enrolled in this study with a Vater Papilla tumor which was in violation of protocol Inclusion Criteria #1: Histologically or cytologically confirmed adenocarcinoma of exocrine pancreas. These protocol violations were reported to the sponsor [Merrimac] and the local Ethics Committee. According to study site communication documentation, the sponsor determined that these subjects were to be excluded from the study analysis. These protocol deviations are reported in the NDA 207793, CSR, Appendix 16.2.2 Protocol Deviations, Listing 16.2.1.5.1; Key Protocol Deviations.

With respect to Site 881, Dr. Li-Tzong Chen, and Site 882, Dr. Chung-Pin Li, the inspections found that there was a leucovorin shortage during the conduct of the study at both of these sites, so some subjects did not receive leucovorin during some of their study visits. According to the FDA field investigator, all missed leucovorin treatments were properly reported in the CSR Key Protocol Deviation data listings correctly. For Site 881 and 882, the proportion of subjects per leucovorin-containing Arms (B and C) affected by the drug shortage was small (between 10 and 20%) and the number of missed leucovorin treatments per subject were similar between the treatment Arms. Therefore, it is unlikely that the leucovorin treatment errors would result in a substantial bias between these Arms. The review division (DOP2) conducted limited sensitivity analyses on October 2, 2015, to assess whether inclusion or exclusion of the affected subjects' data importantly affected study outcome. Dr. Shan Pradham, DOP2 Clinical Reviewer, confirmed on October 2, 2015, that it is unlikely that excluding the subjects in question would have importantly affected the overall study results.

Based on the review of inspectional findings for clinical investigators Dr. Gyorgy Bodoky (Site 366), Dr. Li-Tzong Chen (Site 881), Dr. Andrew Dean (Site 617), Dr. Gayle Jameson (Site 120) and Dr. Chung-Pin Li (Site 882), Study MM-398-07-03-01 data submitted to the Agency generated by these five sites in support of NDA 207793, appear reliable and can be used in support of the application.

Note: Observations noted above are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

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Division of Pediatric and Maternal Health Memorandum

Date: September 22, 2015 **Date Consulted:** May 4, 2015

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Division Director
Division of Pediatric and Maternal Health

To: Office of Hematology and Oncology Products (OHOP)/
Division of Oncology Products 2 (DOP2)

Drug: Onivyde (Irinotecan Liposome Injection) for Intravenous Infusion

Indication: Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin in patients previously treated with gemcitabine

NDA: 207793

Applicant: Merrimack Pharmaceuticals Inc.

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- DPMH consult request dated May 4, 2015, DARRTS Reference ID 3746817
- Sponsor's submitted background package for NDA 207793, Irinotecan Liposome Injection

Consult Question:
"Provide labeling comments for PLLR changes"

INTRODUCTION

On May 4, 2015, Merrimack Pharmaceuticals Inc. submitted 505(b)(2) New Drug Application (NDA) for Irinotecan Liposome Injection, NDA 207793, for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin in patients previously treated with gemcitabine. Orphan designation for treatment of pancreatic cancer was granted on July 21, 2011. Fast Track Designation was granted on November 17, 2014. Camptosar (irinotecan hydrochloride), NDA 20571, the reference listed drug, was originally approved June 14, 1996, for the treatment of refractory colorectal cancer.

The Division of Oncology Products 2 (DOP2) consulted the Division of Pediatric and Maternal Health (DPMH) on May 4, 2015 to review the Pregnancy and Lactation subsections of labeling to ensure compliance with the Pregnancy and Lactation Labeling Rule formatting requirements and to provide comments to be included in the labeling that will be sent to the applicant.

BACKGROUND

Irinotecan and Mechanism of Action

Irinotecan hydrochloride (HCl), which is already an approved drug, is an anti-neoplastic agent and a topoisomerase I inhibitor. Irinotecan and its active metabolite, SN-38, bind reversibly to the topoisomerase I-DNA complex and prevent re-ligation of the single-strand breaks.¹ Irinotecan liposome is made up of irinotecan HCl, the active ingredient, which is encapsulated in a liposome.

When irinotecan liposome is compared to irinotecan HCl, the formation of SN-38 from irinotecan, after infusion of irinotecan liposome, was less than after infusion of irinotecan HCl. The reason for this observation is that most of the irinotecan drug remained in the liposomal form after infusion of irinotecan liposome, limiting the conversion from irinotecan liposome to SN-38. The reader is referred to the Clinical Pharmacology review by Sarah Schrieber, Pharm.D. for further details.

Pancreatic Cancer

Pancreatic cancer accounts for 3% of all cancers in the U.S. and for 7% of cancer deaths. The American Cancer Society estimates that in 2015 there will be 48,960 people diagnosed with pancreatic cancer (24,840 men and 24,120 women), and 40,560 people will die from pancreatic cancer (20,710 men and 19,850 women). Pancreatic cancer occurs in older patients with an average age of diagnosis of 71.² Pancreatic cancer is rare before the age of 40 and is rare during pregnancy.³

¹ Merrimack Pharmaceuticals Draft labeling for Irinotecan Liposome Injection, section 12.1 Mechanism of Action

² <http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-key-statistics>. Accessed 6/3/2015.

³ Blackbourne, et al. Pancreatic adenocarcinoma in the pregnant patient. *Cancer*. 1997. 79(9): 1776-1779.

Pregnancy and Lactation Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”⁴ also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule⁵ format to include information about the risks and benefits of using these products during pregnancy and lactation.

DISCUSSION

Irinotecan and Nonclinical Studies

Animal reproduction studies with irinotecan liposome were not conducted. The applicant used animal reproduction studies conducted for irinotecan HCl, the reference drug. Embryotoxicity and teratogenicity were seen following administration of intravenous irinotecan HCl to pregnant rats and rabbits during organogenesis at doses resulting in irinotecan exposures lower than those achieved with irinotecan liposome 80mg/² in humans. The reader is referred to the Nonclinical Review by Margot Brower, PhD., for further details.

Irinotecan and Pregnancy

No pregnancies occurred during the clinical development program of irinotecan liposome. Since the active ingredient in this drug is irinotecan, the applicant is referencing the previous findings of Camptosar (irinotecan HCl) in regards to pregnancy. The applicant conducted a search of published medical literature using the search terms “irinotecan, pregnancy, genotox and repro-tox” and reviewed several case reports that described the use of irinotecan during pregnancy. In addition, DPMH conducted a search of published literature in Pubmed using the search terms “irinotecan,” “pregnancy,” “miscarriage,” “stillbirth,” “abortion,” and “fetal malformation,” and two relevant articles were found. The case reports regarding the use of irinotecan in pregnancy are discussed below. (See Appendix B for the applicant’s summary of case reports of irinotecan exposure during pregnancy.) In addition, DPMH reviewed periodic adverse drug experience reports for Camptosar (irinotecan) from June 6, 2007 until May 4, 2015, and no pregnancies were reported.

Four case reports discuss the delivery of an infant without a congenital anomaly. The cases are described below.

- A pregnant woman was diagnosed with stage IIIc ovarian adenocarcinoma in the first trimester. Despite two cycles with paclitaxel and carboplatin starting in the 16th week until the 21st week of pregnancy, the patient’s ovarian tumors continued to grow, and a primary colon cancer was found. Four cycles of 5-fluorouracil, irinotecan, and

⁴ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

⁵ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

oxaliplatin were given between gestational weeks 24 to 30. A caesarean section was performed at 32 weeks gestation. The infant was born without congenital anomalies. A slight ventricular dilatation was found via ultrasound on the second day of life and again at one month of age, but there were no clinical symptoms.⁶

- A 33 year-old pregnant woman was diagnosed with adenocarcinoma of the transverse colon with liver and lymph node metastases. She was given irinotecan and fluorouracil from weeks 23 to 28 of pregnancy. However, chemotherapy was stopped when the disease progressed, and the patient underwent an emergency Cesarean section and colon resection at 30 weeks gestation. She delivered a healthy male, and at a 13-month follow-up visit, the child was growing and developing appropriately.⁷
- A 34 year-old woman was diagnosed with a Krukenberg ovarian tumor at 15 weeks gestation. She was treated with surgical removal of the ovary and started 10 courses of chemotherapy (5-fluorouracil, folinic acid and irinotecan) every 2 weeks from week 18 until week 36 of pregnancy. A healthy female infant was born at 37 weeks and 5 days gestation weighing 5lb 14 oz, with Apgar scores of 9 and 9 at 1 and 5 minutes, respectively. The infant was seen one month after delivery and was developing and growing appropriately.⁸
- A pregnant woman with metastatic colorectal cancer was treated with irinotecan and 5-fluorouracil starting at week 23 of pregnancy and delivered a female infant at 25 weeks gestation (reason for early delivery was not noted). The infant was born at 750 grams and had chronic lung disease, ventriculomegaly secondary to a grade 2 intraventricular hemorrhage, patent ductus arteriosus and patent foramen ovale; these conditions were due to prematurity. After discharge and upon follow-up (timing not indicated), the infant had slight developmental delay due to her level of prematurity but otherwise had no congenital anomalies.⁹

Two case reports/case series describe fetal malformations after exposure to irinotecan administered as part of a combination regimen with other chemotherapeutic agents. The cases are described below.

- In a case series, 13 patients with sarcoma were treated with chemotherapy during the course of pregnancy. Of the 13 patients, only one patient was exposed to irinotecan, in combination with oxaliplatin and vinorelbine, in the first trimester of pregnancy and continued irinotecan throughout all three trimesters of pregnancy. This patient delivered an infant at 32 weeks gestation who was found to have a cleft palate and transesophageal fistula.^{10,11}

⁶ Thompson-Bos, et al. Two cases of cancer diagnosis and treatment during pregnancy with favourable outcomes for the babies. *Fundam & Clin Pharmacol*. 2011; 25: 68 (conference publication).

⁷ Cirillo, et al. Irinotecan during pregnancy in metastatic colon cancer. *Tumori*. 2012. 98(6).

⁸ Taylor J, Amanze A, Di Federico E, Verschraegen C. Irinotecan use during pregnancy. *Obstet Gynecol*. 2009;114(2 Pt 2):451–452. (Also included in NPT Monograph)

⁹ Layton T, Soydemir F. A case of metastatic colorectal cancer during pregnancy. *BJOG*. 2014;121(Suppl 6): 50. Abstract 0150.

¹⁰ Azim et al. Treatment of the pregnant mother with cancer: a systemic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy. Part I: Solid tumors. *Cancer Treat Rev*. 2010; 36 (2): 101-9.

¹¹ Abellar RG, Pepperell JR, Greco D, et al. Effects of chemotherapy during pregnancy on the placenta. *Pediatr Dev Pathol*. 2009;12:35–41.

- In a case report, a 37 year old female with rectal carcinoma and liver and lung metastases was being treated with the FOLFIRI-protocol¹² and Avastin (starting at 5 weeks gestation). The pregnancy was not discovered until almost 23 weeks gestation during a CT scan. A male infant was delivered via caesarean section at 36 weeks and was found to have ventricular and atrial septal defects, pulmonary stenosis, poly- and syndactylia of hands, bilateral thumb anomalies and bilateral hip joint luxation.¹³

Reviewer Comments:

Human pregnancy outcome data for irinotecan are limited and confounded by exposure to multiple chemotherapeutic agents with teratogenic potential (i.e. Avastin, 5-fluorouracil) that prevent a clear association with irinotecan. Although there are four case reports of normal pregnancies following exposure to irinotecan, all four women were exposed to irinotecan during the second and third trimesters of pregnancy (ranging between weeks 18 to 36 of gestation) and not during the first trimester of pregnancy when organogenesis occurs. In the two case reports that did demonstrate fetal malformations in the infant, both mothers were exposed to irinotecan, and other chemotherapeutic agents, starting in the first trimester of pregnancy and continued throughout the pregnancy, which suggests that exposure to irinotecan, and other chemotherapeutic agents, in the first trimester may increase the risk of fetal malformations. The likelihood of adverse fetal and infant effects to irinotecan is high based on the drug's mechanism of action and adverse fetal and infant outcomes observed in animal reproduction studies with irinotecan HCl.

Irinotecan and Lactation

The applicant conducted a search of published literature regarding the use of irinotecan during breastfeeding, and no articles were found. DPMH searched the Drugs and Lactation Database (LactMed)¹⁴ and Pubmed for available lactation data on the use of irinotecan, and no information was found. The following serious adverse reactions were observed in adult patients in clinical trials and post-marketing with irinotecan: myelosuppression/neutropenia, diarrhea (complicated by colitis, ulceration, bleeding ileus, colon obstruction, and infection), hepatic impairment, and pulmonary toxicity (interstitial pulmonary disease).

Irinotecan is present in rat milk, and following intravenous administration of radiolabeled irinotecan, radioactivity was present in rat milk and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations.¹⁵

¹² FOLFIRI-protocol: includes treatment with folinic acid, 5-fluorouracil and irinotecan

¹³ Koch S, Wagner D, Hager D. Pregnancy progress in case of metastatic rectum carcinoma under chemotherapy and Avastin doses in early pregnancy. *Arch Gynecol Obstet.* 2010;282(Suppl 1): S220. Abstract PO-Geb 03.32

¹⁴ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

¹⁵ Drugs@FDA. Camptosar Labeling, approved 12/2014. Nursing Mothers: section 8.3.

Reviewer Comments:

The characteristics of irinotecan suggest that the drug may be present in breast milk. Irinotecan has a low molecular weight of 677 Daltons (Drugs with a molecular weight less than 800 Daltons are more likely to pass into breast milk) and a long half-life (irinotecan has a half-life of 26 hours, and the active metabolite SN-38 has a half-life of 68 hours), which increases the presence of the drug in the mother's circulation and may increase infant exposure to the drug via breast milk.¹⁶

Proposed irinotecan lactation labeling states that the drug is not recommended during breastfeeding. Given the risk of potential serious adverse events seen in adult patients in clinical trials with irinotecan, breastfeeding with maternal use of irinotecan is not recommended due to the potential for serious adverse reactions in a breastfed infant. DPMH agrees with the applicant's recommendation against breastfeeding with maternal use of irinotecan.

Irinotecan and Use in Females and Males of Reproductive Potential

Although genotoxicity studies have not been performed for irinotecan liposome, genotoxicity studies with irinotecan HCl in rats showed a trend between the dose of irinotecan HCl and the incidence of uterine horn endometrial stromal polyps and sarcomas. Irinotecan HCl was also clastogenic both *in vitro* (causing chromosome aberrations in Chinese hamster ovary cells) and *in vivo* in mice.

Although fertility studies have not been performed with irinotecan liposome, atrophy of male and female reproductive organs was seen in dogs receiving irinotecan liposome at doses equal to or greater than 9 mg/kg (1.5 times the clinical exposure of irinotecan following irinotecan liposome) for a total of six doses. The reader is referred to the Nonclinical Review by Margot Brower, PhD. for further details.

Reviewer Comments

Due to the potential for adverse fetal and infant effects, females of reproductive potential should use effective contraception during treatment with irinotecan liposome and for one month following completion of therapy to ensure low to no systemic drug levels in a female patient. The duration of contraception use is based on multiplying the half-life of either the drug or the metabolite, whichever is longer, (26 hours is the half-life for irinotecan, and 68 hours is the average half-life for SN-38) by 6.

In males with females of reproductive potential, condoms should be used during treatment with irinotecan liposome and for four months (duration of spermatogenesis, three months, plus one month due to the long half-life) after completion of therapy due to the risk of genotoxicity with irinotecan use.

CONCLUSIONS

DPMH has the following recommendations for irinotecan liposome labeling:

¹⁶ Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. Journal of the American Pharmacists Association. 2012; 51 (1): 86-94.

- **Warnings and Precautions, Section 5.6**
 - Based on the increased likelihood of adverse fetal and infant effects due to the irinotecan liposome’s mechanism of action and embryotoxicity and teratogenicity seen in animal reproduction studies with liposome HCl, a subsection describing embryo- and/or fetal risks (“Embryofetal Toxicity”) as well as mitigation measures must be placed in the Warnings and Precautions section of labeling as required by regulation (21 CFR 201.57(c)(9)(i)(A)(4)).
- **Pregnancy, Section 8.1**
 - The “Pregnancy” subsection of irinotecan liposome labeling was structured in the PLLR format to include the “Risk Summary” and “Data” subsections.¹⁷
- **Lactation, Section 8.2**
 - The “Lactation” subsection of irinotecan liposome labeling was formatted in the PLLR format to include the “Risk Summary” and “Data” subsections.¹⁸
- **Females and Males of Reproductive Potential, Section 8.3**
 - The “Females and Males of Reproductive Potential” subsection of irinotecan liposome labeling was formatted in the PLLR format to include “Contraception” to advise females and males of reproductive potential to use effective contraception during treatment with irinotecan liposome because of the potential for adverse fetal and infant effects from maternal and paternal exposure. This additional subsection is consistent with the PLLR for drugs with a likelihood of embryofetal toxicity.¹⁹
- **Patient Counseling Information, Section 17**
 - The “Patient Counseling Information” section of irinotecan liposome labeling was updated to correspond with changes made to sections 5.6, 8.1, 8.2 and 8.3 of labeling.

RECOMMENDATIONS

DPMH revised subsections 5.6, 8.1, 8.2, 8.3 and 17 of irinotecan liposome labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

¹⁷ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

¹⁸ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

¹⁹ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, C-8.3 Females and Males of Reproductive Potential.

DPMH Proposed Labeling for Irinotecan Liposome Injection

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----WARNINGS AND PRECAUTIONS-----

- Embryofetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception (5.6, 8.1, 8.3)

-----USE IN SPECIFIC POPULATIONS-----

- Lactation: Not recommended (8.2).

FULL PRESCRIBING INFORMATION

5 WARNINGS AND PRECAUTIONS

5.6 Embryofetal Toxicity

Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE 80 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE and for one month following the final dose [*see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman [*see Clinical Pharmacology (12.1)*]. There are no available data with ONIVYDE use in pregnant women. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE 80 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis [*see Data*]. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal data

No animal studies have been conducted to evaluate the effect of irinotecan liposome on reproduction and fetal development; however, studies have been conducted with irinotecan HCl. Irinotecan ^{(b) (4)} crosses the placenta of rats following intravenous administration. Intravenous administration of irinotecan at a dose of 6 mg/kg/day to rats and rabbits during the period of organogenesis resulted in increased post-implantation loss and decreased numbers of live fetuses. In separate studies in rats, this dose resulted in an irinotecan exposure of approximately 0.002 times the exposure of irinotecan based on area under the curve (AUC) in patients administered ONIVYDE at the 80 mg/m² dose. Administration of

irinotecan HCl resulted in structural abnormalities and growth delays in rats at doses greater than 1.2 mg/kg/day (approximately 0.0002 times the clinical exposure to irinotecan in ONIVYDE based on AUC). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan HCl administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring.

8.2 Lactation

Risk Summary

There is no information regarding the presence of irinotecan liposome, irinotecan, or SN-38 (an active metabolite of irinotecan) in human milk, or the effects on the breastfed infant or on milk production. Irinotecan is present in rat milk [*see Data*]. Because of the potential for serious adverse reactions in breastfed infants from ONIVYDE, advise a nursing woman not to breastfeed during treatment with ONIVYDE and for one month after the final dose.

Data

Radioactivity appeared in rat milk within 5 minutes of intravenous administration of radiolabeled irinotecan HCl and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations.

8.3 Females and Males of Reproductive Potential

Contraception

Females

ONIVYDE can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE and for one month after the final dose.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ONIVYDE and for four months after the final dose [*see Nonclinical Toxicology (13.1)*].

17 PATIENT COUNSELING INFORMATION

Embryofetal Toxicity

- (b) (4) females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment and for one month after the final dose, and to inform their healthcare provider of a known or suspected pregnancy [*see Warnings and Precautions (5.6), Use in Specific Populations (8.1, 8.3)*].
- Advise male patients with female partners of reproductive potential to use condoms during treatment with ONIVYDE and for four months after the final dose [*see Females and Males of Reproductive Potential (8.3)*].

Lactation

- Advise women not to breastfeed during treatment with ONIVYDE and for one month after the final dose [*see Use in Special Populations (8.2)*].

APPENDIX A – Applicant’s Proposed Irinotecan Liposome Injection Pregnancy and Lactation Labeling

(b) (4)



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APPENDIX B- Applicant's Review of Published Literature

Table. Summary of Case Reports of Irinotecan Exposure During Human Pregnancy

Irinotecan Dose/Schedule	Study Type	No. of Patients	Cancer Type	Timing of Treatments	Co-Therapy(s)	Gestational Age at Delivery, Weeks	Pregnancy Complications and Outcome(s)	Follow-up Evaluation	Reference
NS	CS	1	Rhabdomyosarcoma	Trimesters 1-3	Oxaliplatin Vinorelbine	32	Weight and Apgar scores NS; cleft lip, cleft palate, tracheoesophageal fistula, esophageal atresia. Placenta had vacuolization and nuclear pleomorphism, extravillous trophoblasts of the chorion leave, villous hypermaturity, and multifocal villous edema	None	Abellar et al, 2009 (also described in Azim et al, 2009)
Q2W, 10 cycles	CR	1	Ovary (Krukenberg)	Trimester 2, 3 First at Wk18 Last at Wk36	5-FU/LV	37 +5 days	Female infant, 5 lb 14 oz, Apgar scores 9 and 9 at 1 and 5 min; infant was born without complications	At 4 mo, development was normal with no teratogenic effects	Taylor et al, 2009
FUFIRI (dose and schedule NS)	CR	1	mCRC	Trimester 1, 2 (3 rd NS) First at Wk5+2	5FU/LV Bevacizumab	36 +4 days	Male infant, 1770 g, length 42 cm, head circumference 32.5 cm; hypotrophic in a moderate diminished general condition of health; drink laziness; atrial and ventricular septal defects, pulmonary stenosis, poly- and syndactylia of both hands, both thumbs anomaly and both hips joint luxation	NS	Koch et al, 2010
FOLFIRINOX Q2W, 4 cycles (2 paclitaxel /carboplatin cycles prior)	CR	1	Ovary (IIIc)	Trimester 2, 3 First at Wk24 Last at Wk30	5-FU/LV, Oxaliplatin Lenograstim	32	Weight and Apgar scores NS; Day 2 - slight ventricular dilatation (ultrasonography)	At 1 mo, ventricular dilatation via US, but noted as not clinically significant	Thompson-Bog et al, 2011
FOLFIRI Q2W, 3 cycles	CR	1	mCRC	Trimester 2, 3 First at Wk23 Last at Wk27	5-FU/LV	30	Male infant, 1070 gm; Apgar score of 4 and 7 at 1 and 5 min; no significant findings, no fetal drug toxicity observed at birth	At 13 mo, all appropriate growth and developmental milestones were achieved	Cinillo et al, 2012
FOLFIRI (Q2W, IrMdg)	CR	1	mCRC	Trimester 2 First at Wk23 Last NS	5-FU/LV	25	Female infant, 750 g; Chronic lung disease, ventriculomegaly secondary to bilateral grade 2 intraventricular hemorrhage, patent ductus arteriosus and patent foramen ovale; no teratogenic effects were noted	Continued to do well; examination revealed slight delay appropriate for level of prematurity	Layton et al, 2014

5-FU=5-fluorouracil; CR = case report; CS = case series; IrMdg = Irinotecan/modified de Gramont; mCRC = metastatic colorectal cancer; NS = not specified; US = ultrasound.

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/s/

MIRIAM C DINATALE
09/22/2015

TAMARA N JOHNSON
09/23/2015

LYNNE P YAO
09/23/2015

LABEL AND LABELING REVIEW

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: July 27, 2015
Requesting Office or Division: Division of Oncology Products 2 (DOP2)
Application Type and Number: NDA 207793
Product Name and Strength: Onivyde (irinotecan liposome injection),
50 mg/10 mL (5 mg/mL)
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Merrimack Pharmaceuticals, Inc.
Submission Date: April 24, 2015, May 29, 2015, and
June 30, 2015, July 14, 2015, and July 16, 2015
OSE RCM #: 2015-473
DMEPA Primary Reviewer: Otto L. Townsend, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of the NDA review process for Onivyde, DOP2 requested that we review the proposed container labels, carton labeling, and Prescribing Information for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

If approved, this Application will introduce a new liposomal formulation of irinotecan hydrochloride. We note this new liposomal formulation of irinotecan could be confused with the listed drug product, Camptosar (irinotecan hydrochloride – NDA 020571). If the recommended dosage for irinotecan hydrochloride liposome injection (80 mg/m²) is confused with that of irinotecan hydrochloride (up to 180 mg/m²), a patient could receive an overdose that is 2.25 times the recommended dose. Alternatively, if a patient received treatment with Camptosar with the dose based on Onivyde, the patient would receive an underdose and possibly not receive the full clinical benefit of therapy.

A similar risk of confusion exists with the drug products, Doxil (doxorubicin hydrochloride liposome injection) and doxorubicin hydrochloride. The labeling strategies to address the risk of potential confusion between the liposomal and conventional doxorubicin formulations include the following statement in the Dosage and Administration section of the Prescribing Information (PI), “Do not substitute DOXIL for doxorubicin HCl injection.” The Applicant has proposed a similar statement for the Onivyde PI, which states, “DO NOT SUBSTITUTE ONIVYDE for (b) (4) other drug (b) (4) containing irinotecan.” In addition, Doxil container label and

carton labeling contain the following warning, “LIPOSOMAL FORMULATION – DO NOT SUBSTITUTE FOR DOXORUBICIN HCL”. Similarly, proposed Onivyde container label and carton labeling propose the following statement, “(b) (4)”, be placed on container label and carton labeling. These warnings appear sufficient to address the risk of confusion between the listed drug, irinotecan hydrochloride (Camptosar) and the proposed liposomal product, Onivyde.

4 CONCLUSION & RECOMMENDATIONS

The proposed prescribing information (PI), container labels, and carton labeling can be improved to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. The Applicant uses passive voice throughout the PI. We defer to the review team to determine if revision to active voice should be requested.
2. If a final infusion solution total volume of 500 mL is not required to maintain stability of the infusion solution, we recommend changing the preparation statement (Section 2.3) to read, “Add the required volume of ONIVYDE to 500 mL of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP. Mix diluted solution by gentle inversion.”

4.2 RECOMMENDATIONS FOR MERRIMACK

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container label and carton labeling)

1. Decrease the size and prominence of the green logo, and consider relocating to a location that does not compete in prominence. Critical product information, such as the proprietary name, should be the most prominent information on the principal display panel (PDP). Other information on the PDP such as manufacturer logo should not compete in size and prominence with important product information¹.
2. To strengthen the cautionary statement, “(b) (4)”, change the statement to read, “LIPOSOMAL FORMULATION DO NOT SUBSTITUTE FOR IRINOTECAN HYDROCHLORIDE.” Consider using sentence

¹ Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance). April 2013.

case or only capitalizing the first letter because words written in all-capital letters are less legible than words written in mixed case letters.

3. To emphasize the action required from the user, use bold font for the statement, "Refrigerate at 2°C to 8°C (36°F to 36°F)." In addition, remove bold font for the statement, "Do not freeze."
4. Change the strength statement from:
50 mg in a 10 mL vial
(5 mg/mL)

to,

50 mg/10 mL
(5 mg/mL)

Please note the strength, 50 mg/10 mL, is bolded; and the concentration, 5 mg/mL, is not bolded.

B. Container Label

1. The proposed container label lacks a linear barcode. Please add a barcode as described in 21 CFR 201.25.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Onivyde that Merrimack submitted on July 14, 2015, and the listed drug (LD).

Table 2. Relevant Product Information for Onivyde and the Listed Drug		
Product Name	Onivyde	Camptosar
Initial Approval Date	N/A	June 14, 1996
Active Ingredient	Irinotecan Liposome	Irinotecan hydrochloride
Indication	Treatment of metastatic adenocarcinoma of the pancreas, in combination with fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine-based therapy.	First-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum and treatment of metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	Injection
Strength	50 mg/10 mL (5 mg/mL)	40 mg/2 mL and 100 mg/5 mL (20 mg/mL)
Dose and Frequency	80 mg/m ² intravenous infusion over 90 minutes, every 2 weeks, followed by leucovorin 400 mg/m ² infusion over 30 minutes followed by fluorouracil 2400 mg/m ² infusion over 46 hours.	Colorectal cancer combination regimen 1: CAMPTOSAR 125 mg/m ² intravenous infusion over 90 minutes on days 1, 8,15, 22 with LV 20 mg/m ² intravenous bolus infusion on days 1, 8, 15, 22 followed by 5-FU intravenous bolus infusion on days 1, 8, 15, 22 every 6 weeks. Colorectal cancer combination regimen 2: CAMPTOSAR 180 mg/m ² intravenous infusion over

		<p>90 minutes on days 1, 15, 29 with LV 200 mg/m² intravenous infusion over 2 hours on days 1, 2, 15, 16, 29, 30 followed by 5-FU 400 mg/m² intravenous bolus infusion on days 1, 2, 15, 16, 29, 30 and 5-FU 600 mg/m² intravenous infusion over 22 hours on days 1, 2, 15, 16, 29, 30.</p> <p>Colorectal cancer single agent regimen 1: CAMPTOSAR 125 mg/m² intravenous infusion over 90 minutes on days 1, 8, 15, 22 then 2-week rest.</p> <p>Colorectal cancer single agent regimen 2: CAMPTOSAR 350 mg/m² intravenous infusion over 90 minutes on day 1 every 3 weeks.</p>
How Supplied	Single-use vial	Single-dose vial
Storage	Store at 2°C to 8°C (36°F to 46°F). Do NOT freeze. Protect from light.	Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. Keep the vial in the carton until the time of use.
Container Closure	10 mL Type I clear glass vial	Amber colored polypropylene CYTOSAFE® vials.

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/s/

OTTO L TOWNSEND
07/27/2015

CHI-MING TU
07/27/2015



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: July 8, 2015

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Deanne Varney, RPM
DOP2

Subject: QT-IRT Consult to NDA 207793

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 6/23/2015 regarding the adequacy of QT assessment in the ongoing trial CITS for fulfilling the regulatory requirement of QT assessment for ONIVYDE. The QT-IRT received and reviewed the following materials:

- Your consult
- Clinical study protocol: CITS (MM-398-01-01-02)
- QT-IRT's previous review (dated 6/22/2015)

QT-IRT Comments for DOP2

The QT assessment in the ongoing trial CITS (MM-398-01-01-02) will not contribute to understanding QT effects of ONIVYDE. ECG/PK monitoring should be collected at baseline, after first dose, and at steady state around T_{max} for irinotecan.

BACKGROUND

ONIVYDE (irinotecan liposome injection, MM-398) is indicated for the treatment of metastatic adenocarcinoma of the pancreas. We previously evaluated the data included in this new NDA submission and commented that *“There is no adequate assessment of irinotecan on QT prolongation. We have no recommendation for labeling at this stage. A PMR should be*

requested according to the ICH E14 guidance. Adequate ECG/PK monitoring should be collected at baseline, after first dose, at steady state around Tmax for irinotecan. The ongoing trial CITS may be able to fulfill the requirement of QT assessment for ONIVYDE. Please submit the protocol of CITS for our further review.”

In the current consult, the study protocol of the ongoing trial CITS (MM-398-01-01-02) was provided to us:



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Thank you for requesting our input into the development of this product under NDA 207793. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

JIANG LIU
07/08/2015

NORMAN L STOCKBRIDGE
07/08/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 207793 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Onivyde (proposed) Established/Proper Name: Irinotecan Liposome Injection Dosage Form: Injection Strengths: 50 mg/10 mL		
Applicant: Merrimack Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: April 24, 2015 Date of Receipt: April 24, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: October 24, 2015		Action Goal Date (if different):
Filing Date: June 23, 2015		Date of Filing Meeting: May 12, 2015
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input checked="" type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
The application will be a priority review if:	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 102799

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Email sent 5/5/15
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm		<input type="checkbox"/>	<input checked="" type="checkbox"/>		No unexpired exclusivity for this active moiety. There are unexpired patents but the applicant is claiming Section VIII – MOU certification and states that Patents 6403569 and 6794370 do not claim a use for which they are seeking approval
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDAs/NDA efficacy supplements only: Has the applicant	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment

PREA				
Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Orphan designation received July 21, 2011 – exempt from PREA requirements
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BPCA:				
Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

	<input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent: Maternal Health (5/4/2015) OSI (4/27/2015) QT-IRT (5/4/2015)</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): August 19, 2011 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): December 2, 2014 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 12, 2015

BLA/NDA/Supp #: 207793

PROPRIETARY NAME: Onivyde (proposed)

ESTABLISHED/PROPER NAME: irinotecan liposome injection

APPLICANT: Merrimack Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine

BACKGROUND: An EOP2 meeting was held on August 19, 2011, and a pre-NDA meeting was held on December 2, 2014.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Deanne Varney	Y
	CPMS/TL:	Monica Hughes	N
Cross-Discipline Team Leader (CDTL)	Steven Lemery		Y
Division Director/Deputy	Patricia Keegan		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Shan Pradhan	Y
	TL:	Steven Lemery	Y
Clinical Pharmacology	Reviewer:	Sarah Schrieber	Y
	TL:	Gene Williams	Y
Biostatistics	Reviewer:	Hui Zhang	Y
	TL:	Kun He	N

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Margot Brower	N
	TL:	Whitney Helms	Y
Product Quality (CMC) Review Team:	ATL:	Liang Zhou	Y
	RBPM:	Rabiya Laiq	Y
• Drug Substance	Reviewer:	Ray Frankewich	N
• Drug Product	Reviewer:	Mike Adams	N
• Process	Reviewer:	Sung Kim	N
• Microbiology	Reviewer:	Haijing Hu	N
• Facility	Reviewer:	Michael Shanks	N
• Biopharmaceutics	Reviewer:	Banu Zolnik	N
• Immunogenicity	Reviewer:		N
• Labeling (BLAs only)	Reviewer:		N
• Other (e.g., Branch Chiefs, EA Reviewer)	QAL – Liang Zhou Branch Chief – Olen Stephens		N
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Otto Townsend	Y
	TL:	Alice Tu	N
OSE/DRISK (REMS)	Reviewer:	Naomi Redd	N
	TL:	Doris Auth	N

Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Conner	Y
	TL:	Susan Thompson	N
Genomics	Reviewer:	Anuradha Ramamoorthy	Y
	TL:	Rosane Charlab Orbach	Y
Pharmacometrics	Reviewer:	Anshu Marathe	Y
	TL:		
Biopharmaceutics	Reviewer:	Banu Zolnik	Y
	TL:	Okpo Eradiri	N
Other attendees	None		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO PK data in patients
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: Application is missing datasets for six studies. Team will contact Merrimack to request missing datasets.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) 	<input type="checkbox"/> YES

needed?	<input checked="" type="checkbox"/> NO
BIOSTATISTICS Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> • Is the product an NME?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Patricia Keegan, M.D.	

Date of Mid-Cycle Meeting: July 20, 2015

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Proposed labeling to applicant: October 3, 2015

Primary Reviews: September 30, 2015

Secondary Reviews: October 3, 2015

CDTL Review: October 10, 2015

Signatory Review: October 24, 2015

Comments: The following was discussed during the filing meeting:

1. Priority review will be granted.
2. A decision regarding ODAC is pending based on input from future SGE consults
3. The mid-cycle meeting will be held July 20th and labeling meetings are scheduled in late July – early September.
4. Clinical sites have been selected for inspection and inspections are being scheduled.

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review

ACTION ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter

<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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

/s/

DEANNE R VARNEY
07/02/2015

**REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 207793

Application Type: New 505(b)(2) NDA

Name of Drug/Dosage Form: Onivyde [*proposed*] (irinotecan liposome injection)

Applicant: Merrimack Pharmaceuticals, Inc.

Receipt Date: April 24, 2015

Goal Date: October 24, 2015

1. Regulatory History and Applicant's Main Proposals

This application proposes irinotecan liposome injection as a treatment for metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine.

The clinical development occurred under IND 102799. An EOP2 meeting was held on August 19, 2011 and a pre-NDA meeting was held on December 2, 2014.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

Additional labeling issues were identified as noted in the attached PI.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the filing letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by July 13, 2015. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present

Selected Requirements of Prescribing Information

• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **“HIGHLIGHTS OF PRESCRIBING INFORMATION”**.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: **“These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).”** The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement **“Initial U.S. Approval:”** followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment:

- YES** 13. The BW must have a heading in UPPER CASE, containing the word **“WARNING”** (even if more than one warning, the term, **“WARNING”** and not **“WARNINGS”** should be used) and other words to identify the subject of the warning (e.g., **“WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”**). The BW heading should be centered.

Comment:

- YES** 14. The BW must always have the verbatim statement **“*See full prescribing information for complete boxed warning.*”** This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

YES

Selected Requirements of Prescribing Information

15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- NO** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: *Established pharmacologic class not included*

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

Selected Requirements of Prescribing Information

- NO** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: Complete phone number not provided for manufacturer

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

Comment:

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment: *The only listed contraindication is hypersensitivity to irinotecan. A contraindication in patients with hypersensitivity reactions should be included only when there are demonstrated cases of hypersensitivity with the product or such reactions may be anticipated based on data from similar pharmacological class with similar chemical structures.*

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *No patient labeling for this product.*

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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

/s/

DEANNE R VARNEY
07/02/2015



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 22, 2015

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Deanne Varney, RPM
DOP2

Subject: QT-IRT Consult to NDA 207793

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 5/4/2015 regarding the sponsor's QT assessment of Irinotecan Liposome Injection in the NDA submission. The QT-IRT received and reviewed the following materials:

- Your consult
- Clinical safety summary
- Clinical study report: MM-398-07-03-01 (NAPOLI-1)
- Clinical overview
- Highlights of clinical pharmacology and cardiac safety
- The proposed label

QT-IRT Comments for DOP2

We are requesting a QT-IRT reviewer to: evaluate the data included in this new NDA submission; comment on the need for labeling, and if so, provide draft language for consideration; if there is insufficient data, advise whether or not a PMR should be requested and provide draft PMR language for consideration.

QT-IRT's response: There is no adequate assessment of irinotecan on QT prolongation. We have no recommendation for labeling at this stage. A PMR should be requested according to the ICH E14 guidance. Adequate ECG/PK monitoring should be collected at baseline, after first dose, at steady state around Tmax for irinotecan. The ongoing trial CITS may be able to fulfill the requirement of QT assessment for ONIVYDE. Please submit the protocol of CITS for our further review.

BACKGROUND

ONIVYDE (irinotecan liposome injection, MM-398) is indicated for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in patients who have been previously treated with gemcitabine. The active ingredient in ONIVYDE is irinotecan, which is encapsulated in a long-circulating liposome. Irinotecan is a derivative of camptothecin. Irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase I-DNA complex and prevent re-ligation of these single-strand breaks. The recommended dose and regimen is ONIVYDE 80 mg/m² intravenously over 90 minutes, followed by LV 400 mg/m² intravenously over 30 minutes, followed by 5-FU 2400 mg/m² intravenously over 46 hours, administered every 2 weeks.

Preclinical cardiac safety: In a single dose safety pharmacology study (NDA Module 2.6.2.4.2.1. Study No. 20036143), electrocardiograms (ECG) were evaluated at 4 and 0.5 hours prior to dosing and 0.5, 2.5, 4 and 24 hours after the start of dosing, which included the time points around Cmax of irinotecan and SN-38. There were no MM-398-related changes in cardiovascular hemodynamic or electrocardiographic parameters, including heart rate, rhythm, and conduction, arterial blood pressure, or RR, ORS PR QT and QTca intervals at single dose levels up to 21 mg/kg MM-398. In a 4-week repeat toxicity dose study (NDA Module 2.6.6.3.2.1. Study No. PEP02-NC-G-Tx-009 (6152)), 4, 8, and 16 mg/kg MM-398 was given as a 90 minute intravenous infusion to beagle dogs once weekly for 28 days, with a 14-day recovery period. Heart rate, rhythm, and conduction, and electrocardiograms (limb leads I, II and III, and augmented leads aVR, aVL and aVF) were obtained for each dog (both study phases) once during the pre-treatment week, prior to dosing on each of Days 1 and 22, and at approximately 1 and 6 hours following the conclusion of the 90 minute infusion period on each dosing day. Neither the morphology of the electrocardiographic tracings nor the derived data comprising the cardiac profiles, including heart rate, PR interval, QRS duration and both QT and QTc intervals, revealed evidence of an effect of MM-398 at dose levels up to 16 mg/kg once weekly for 4 weeks.

Clinical Cardiac Safety: No formal QTc evaluation study was conducted during ONIVYDE clinical development because of the lack of evidence of cardiac toxicity in pre-clinical studies with MM-398 and because irinotecan is not known to cause QTc prolongation. Furthermore, in the PEP0206 study, PK profiles of MM-398 (120 mg/m²) and Camptosar® (300 mg/m²) were compared in patients treated for advanced gastric cancers. AUC_{0-∞} of SN-38, the active metabolite of irinotecan, was only marginally higher following the administration of MM-398 than Camptosar® (1.4-fold), and more importantly, Cmax of SN-38 was lowered more than 5.3-fold. Therefore, the existing knowledge about irinotecan cardiac safety is applicable for MM-398.

In the clinical development program, the following studies had QTc measurements recorded in the clinical database, with timepoints indicated:

- PEP0201: An electrocardiogram (ECG) was performed at screening, at the end of each course and at the end of study treatment.
- NAPOLI-1: ECG was performed at screening and at the 30-day follow-up. Also was performed as clinically indicated during the study.
- CITS (ongoing): [REDACTED] (b) (4)

The following QT-related language were provided in the Clinical Safety Summary:

2.7.4.4.2 Potential Effects on ECG and QTc Interval

In the NAPOLI-1 study, there were no clinically significant changes in ECG parameters. ECGs were assessed at baseline and at 30 day follow-up. In addition, for those patients with QTc evaluations, there were no clinically significant changes in QTc interval in the limited ECGs collected during the study. There were no notable ECG observations in other studies.

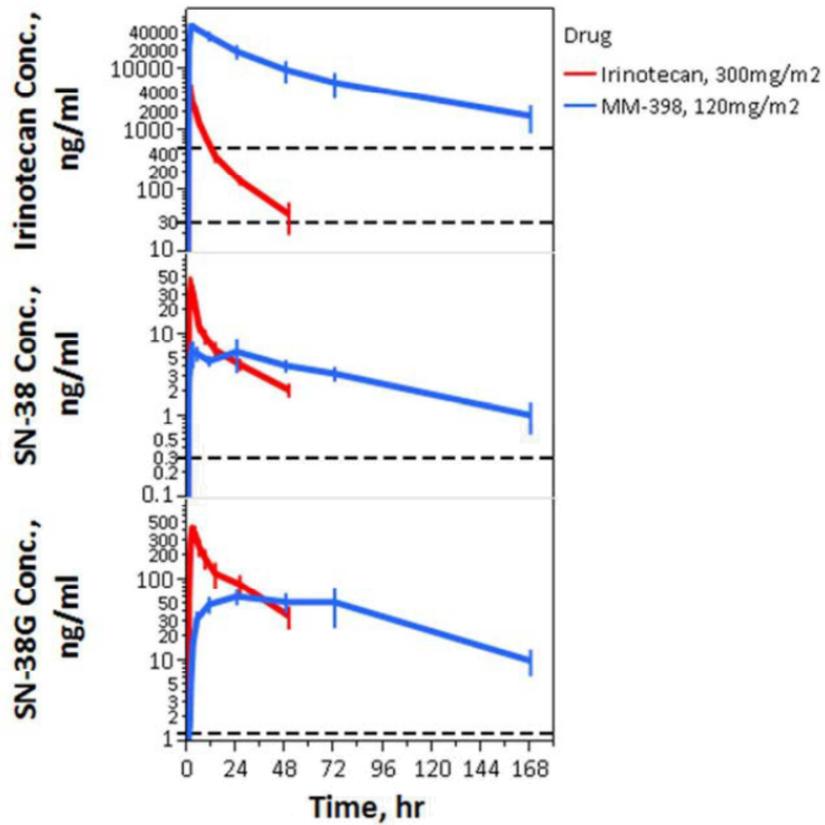
Table 14.3.4.7
QTc Interval Prolongation
Safety Population

Visit	ECG: QTc Result	MM-398 (N=147)	MM-398+5-FU/LV (N=117)	5-FU/LV (N=134)
Baseline	# with QTc assessed	125	96	112
	QTc > 500 msec	3 (2.4)	0	2 (1.8)
	QTc > 480 msec and =< 500 msec	1 (0.8)	0	2 (1.8)
	QTc > 450 msec and =< 480 msec	10 (8.0)	7 (7.3)	3 (2.7)
30-Day- Follow-Up	# with QTc assessed	53	39	45
	QTc > 500 msec	1 (1.9)	1 (2.6)	0
	QTc > 480 msec and =< 500 msec	0	0	0
	QTc > 450 msec and =< 480 msec	3 (5.7)	2 (5.1)	3 (6.7)
QTc change from Baseline to 30-Day-Follow-Up	# with QTc assess at BL and 30-day FU	53	35	44
	> 60 msec	1 (1.9)	1 (2.9)	0
	> 30 =< 60 msec	4 (7.5)	4 (11.4)	4 (9.1)

Source: NAPOLI-1 CSR, Table 14.3.4.7

Reviewer's comments: The direct comparison of the pharmacokinetics of irinotecan and SN-38 in patients administered ONIVYDE 120 mg/m² q3w or conventional irinotecan 300 mg/m² (Camptosar, approved in 1996) q3w was evaluated in Study PEP0206 (Module 2.7.2 Summary Clinical Pharmacology/Section 2.7.2.2.4). Compared to the administration of conventional irinotecan 300 mg/m² q3w, administration of ONIVYDE 120 mg/m² q3w resulted in higher exposure of total irinotecan (C_{max} 13.4-fold and AUC_{0-∞} 46.2-fold; all comparison values were not dose-normalized), higher SN-38 AUC_{0-∞} (1.4-fold), however, SN-38 C_{max} was reduced (0.19-fold). Therefore, the QT effect of irinotecan in ONIVYDE should be further evaluated, although additional assessment of the QT effect of SN-38 does not seem to be needed. The ongoing trial CITS may be able to fulfill the requirement of QT assessment for ONIVYDE.

Figure 3-1: Mean concentrations of total irinotecan, SN-38 and SN-38G over one week after the administration of either MM-398 (120mg/m²) or irinotecan (300mg/m²) in Study PEP0206



Source: Clinical Overview, Page 13.

Thank you for requesting our input into the development of this product under NDA 207793. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrdpqt@fda.hhs.gov

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/s/

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