

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207793Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	October 22, 2015
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	NDA 207793
Applicant Name	Merrimack Pharmaceuticals, Inc.
Date of Submission	April 24, 2015
PDUFA Goal Date	October 24, 2015
Proprietary Name / Established (USAN) Name	Onivyde/ irinotecan liposome injection
Dosage Forms / Strength	Injection for intravenous use/
Proposed Indication(s)	“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”
Action:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Regulatory Project Manager Review	Deanne Varney
Medical Officer Review	Shan Pradhan
Statistical Review	Huanyu (Jade) Chen
Pharmacology Toxicology Review	Margaret Brower
Quality Review	Olen Stephens (Technical Lead); William M. Adams; Ray Frankewich; Sung Kim
Quality Microbiology Review	Denise A Miller
Facility Review	Michael R. Shanks
Quality Biopharmaceutics Review	Banu Sizanli Zolnik
Clinical Pharmacology Review	Sarah Schrieber
CDTL Review	Steven Lemery
OPDP	Carole Broadnax
OSI	Lauren Iacono-Connors
OSE/DMEPA	Otto Townsend
QT IRT Review	Jiang Liu
DPMH Review	Miriam Dinatale

OND=Office of New Drugs
 OPDP=Office of Prescription Drug Promotion
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 OSI=Office of Scientific Investigations
 IRT=Interdisciplinary Review Team
 DPMH=Division of Pediatric and Maternal Health
 CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

This NDA was submitted under the provisions of 505(b)(2) and relies on FDA's prior findings of safety and effectiveness for listed drug Camptosar (irinotecan hydrochloride injection, Pfizer), which was approved under NDA 20571. The application contains pharmacokinetic data to provide the bridging data supporting the scientific appropriateness of such reliance.

Merrimack is seeking approval for the following proposed indication, for which the reference listed drug is not approved. Merrimack has not requested approval of irinotecan liposome for the approved indications of the referenced listed drug.

In support of this NDA, the results of a single, multi-center, randomized, open-label, active-controlled, three-arm trial (NAPOLI) enrolling 417 patients with metastatic pancreatic adenocarcinoma with documented disease progression after gemcitabine-based therapy. Patients were randomly allocated (1:1:1) to receive irinotecan liposome in combination with 5FU and LV (n=117), irinotecan liposome (n=151), or 5FU and LV (n=149) until disease progression or unacceptable toxicity. Patients homozygous for the UGT1A1*28 allele initiated treatment with irinotecan liposome at a reduced dose in the two irinotecan liposome-containing arms. The primary study endpoint was OS, with comparisons of each of the two irinotecan liposome-containing arms with the 5FU/LV control arm; progression-free survival (PFS) and overall response rate (ORR) were secondary endpoints.

The NAPOLI trial demonstrated a statistically significant improvement in OS [HR 0.68 (95% CI: 0.50, 0.93), p=0.014, log-rank test] for patients randomized to receive irinotecan liposome in combination with 5FU and LV compared to those randomized to receive 5FU/LV; the median OS was 6.1 and 4.2 months, respectively. PFS was also significantly longer in patients randomized to receive irinotecan liposome plus 5FU/ LV compared to those randomized to receive 5FU/LV [HR 0.55 (95% CI: 0.41, 0.75)], with median PFS of 3.1 and 1.5 months, respectively. The ORR was low in both arms (7.7% vs. 0.8%). There was no improvement in OS for patients randomized to receive irinotecan liposome alone compared to those randomized to receive 5FU/LV [hazard ratio=1.00, p =0.97].

Serious risks of irinotecan liposome identified in this trial, supplemented by 148 patients in dose-finding and activity-estimating trials, as well as FDA's prior findings of safety and effectiveness for the reference listed drug, are neutropenic fever or sepsis, severe diarrhea, and interstitial lung disease. Severe hypersensitivity reactions have occurred with irinotecan hydrochloride; irinotecan liposome injection is contraindicated in patients with severe allergic reactions to irinotecan liposome or irinotecan hydrochloride. The most common adverse drug reactions were diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common severe (Grade 3-4) laboratory abnormalities were lymphopenia, and neutropenia. The most frequent adverse reactions resulting in discontinuation of

irinotecan liposome were diarrhea, vomiting, and sepsis. The most frequent adverse reactions leading to dose reductions or delays were neutropenia, diarrhea, nausea/vomiting, anemia, fatigue, and thrombocytopenia.

Issues considered during review of this application were the appropriate manner in which to describe the product strength, in light of the USP Salt Policy, and the acceptability of the control arm in the NAPOLI trial, which used a similar but not identical fluorouracil and leucovorin regimen than in the irinotecan, fluorouracil, and leucovorin. These issues are discussed in greater detail in Sections 3 and in Sections 7 and 10 of this Summary Review.

2. Background

Indicated Population and Available Therapy

Based on the Surveillance and Epidemiology and End Results (SEER) epidemiologic data, an estimated 48,960 new cases and 40,560 deaths due to pancreatic adenocarcinoma are anticipated in the U.S. in 2015.¹ Approximately half (53%) of new cases are metastatic at diagnosis; the 5-year survival rates for patients with metastatic disease is 2.4%. There are five drugs which are currently FDA-approved for the treatment of pancreatic cancer;

Gemcitabine was approved on May 15, 1996 for “as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemcitabine is indicated for patients previously treated with 5-FU.” Approval was based on improvement in “clinical benefit” response rate, survival, and time-to-progression in a randomized trial comparing gemcitabine with 5-fluorouracil (5-FU) in patients who had received no prior chemotherapy.

Erlotinib was approved on November 2, 2005, for use “in combination with gemcitabine, for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.” Approval was based on demonstration of improved survival in a randomized, trial comparing erlotinib plus gemcitabine to gemcitabine alone.

Paclitaxel protein-bound particles for injectable suspension (albumin-bound) was approved on September 6, 2013 for “the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.” Approval was based on the results of a randomized trial demonstrating improvement in overall survival, progression-free survival, and overall response for those randomized to paclitaxel protein-bound particles with gemcitabine compared with those randomized to gemcitabine alone.

Fluorouracil was approved in 1962. The indications and usage section of labeling states “Fluorouracil is effective in the palliative management of carcinoma of the pancreas. The basis for approval is not described in product labeling.

¹ <http://seer.cancer.gov/statfacts/html/pancreas.html>

Mitomycin is no longer marketed in the U.S. It was approved for the following indication
“Mitomycin is not recommended as single-agent, primary therapy. It has been shown to be useful in the therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed.”

In addition to the FDA-approved drugs discussed above, the combination chemotherapy regimen of FOLFIRINOX is recommended by the NCCN for the first-line treatment of good performance status patients with metastatic pancreatic cancer, based on the published results by Conroy, et al.² In this trial, 342 patients with metastatic pancreatic cancer and an Eastern Cooperative Oncology Group performance status score of 0 or 1 were randomized to receive FOLFIRINOX (oxaliplatin, 85 mg² body-surface area; irinotecan, 180 mg²; leucovorin, 400 mg²; and fluorouracil, 400 mg² given as a bolus followed by 2400 mg² given as a 46-hour continuous infusion, every 2 weeks) or gemcitabine at the approved dose and schedule for pancreatic cancer.

As reported by Conroy, the trial demonstrated a statistically significant improvement in the primary endpoint of overall survival [HR 0.57 (95% CI 0.45, 0.73); p<0.001] with median survival times of 11.1 months in the FOLFIRINOX arm and 6.8 months in the gemcitabine arm. The trial also demonstrated a significant improvement in progression-free survival (HR 0.47 (95% CI: 0.37, 0.59); p<0.001) with median PFS times of 6.4 months and 3.3 months in the FOLFIRINOX and gemcitabine arms, respectively and a significant improvement in overall response rate (31.6% vs. 9.4%) for FOLFIRINOX.

The NCCN practice guidelines recommend combination chemotherapy with gemcitabine plus Abraxane (paclitaxel protein-bound particles for injectable suspension (albumin-bound)) or with FOLFIRINOX combination chemotherapy based on demonstration of a survival advantage gemcitabine alone as the initial treatment for unresectable disease. Additional regimens include which are considered reasonable include gemcitabine alone or in combination with erlotinib, capecitabine, infusional 5-fluorouracil, or a fluoropyrimidine in combination with oxaliplatin are acceptable first-line regimens. For patients receiving second-line chemotherapy following treatment with gemcitabine (the population studied in the NAPOLI trial), NCCN guidelines recommends enrollment in a clinical trial or treatment with fluoropyrimidine-based chemotherapy.

Based on the lack of FDA-approved therapy for treatment of patients with disease progression following a gemcitabine-based chemotherapy regimen, available therapy is limited to fluoropyrimidine-based chemotherapy, the control arm of the NAPOLI trial.

Pre-Submission Regulatory History

September 18, 2008: A preIND meeting was held with PharmaEngine to discuss the planned development program for irinotecan liposome for the treatment of pancreatic cancer in a single arm, activity estimating trial. Irinotecan liposome was developed at Hermes

² Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *NEJM*. 2011 364(19):1817-25.

Biosciences, Inc. (CA) and licensed to PharmaEngine, Inc. of Taiwan, for clinical development. PharmaEngine initiated first-in-man clinical trials in January 2005, in Taiwan. Key discussion and agreements include:

- FDA advised that an *in vitro* test and specification be developed for release of drug substance from the liposome in human plasma or in an appropriate simulated physiological medium.
- FDA requested that assays of lipid components in the drug product and determination of the (b) (4) ratio be incorporated as drug product specifications and to provide stability data in the IND.
- FDA confirmed that no additional preclinical studies appear to be needed to support the proposed study based on completed preclinical studies and the dose-finding clinical study conducted in Taiwan.
- FDA stated that safety pharmacology studies would be required in the NDA but could be conducted concurrent with the conduct of the major efficacy trials. An embryo-fetal developmental toxicity study would not be required.
- FDA advised that the pharmacokinetics be determined for all of the drugs in an irinotecan liposome-containing regimen and that renal and hepatic impairment studies be conducted with irinotecan liposome since differences in the relative contributions of elimination and excretion pathways may be formulation dependent. Drug interactions studies would not be required based on prior finding of safety and effectiveness with irinotecan hydrochloride since the pathways with which irinotecan interacts are unlikely to be formulation-dependent.

IND 102799 was submitted on October 13, 2008, sponsored by PharmaEngine, and was allowed to proceed on November 13, 2008.

In June 2011, sponsorship of IND 102799 was transferred to Merrimack Pharmaceuticals, Inc.

July 21, 2011: FDA granted orphan drug designation for irinotecan liposome for the treatment of pancreatic cancer.

On August 19, 2011, an end-of-Phase 2 meeting was held to discuss the proposed trial intended to support a planned NDA and the proposed plan to bridge data across changes in the manufacturing program. Key agreements and discussions were:

- FDA agreed that if the analytical comparability studies show no significant changes in product derived from the two manufacturing sites, additional no non-clinical, clinical pharmacokinetic, or bioavailability studies would be required.
- FDA agreed with the clinical pharmacology development plan to provide studies investigating inter-patient pharmacokinetic variability and exposure-response relationships for efficacy and toxicity.
- With regard to the proposed trial, a randomized (1:1), open-label trial designed to show superior overall survival for irinotecan liposome (b) (4) mg/m² to fluorouracil 2000 mg plus leucovorin 200 mg/m² in 250 patients with pancreatic cancer with disease progression following gemcitabine-based chemotherapy could, supported by the early activity-estimating trial, potentially provide sufficient safety and effectiveness for the planned NDA.

- FDA did not object to the control arm but expressed concern regarding the timing and significance level of the planned interim analysis, recommended that an unstratified analysis be used given the small size of the trial, and noted that an additional trial may be required if the single trial did not demonstrate statistically robust results. Based on the results of Protocol PEP0206, FDA advised that the initial dose of liposomal irinotecan be reduced in patients homozygous UGT1A1*28, however FDA also requested that pharmacokinetic data be submitted to the IND.

November 8, 2013: FDA issued an Advice memorandum informing Merrimack that, following evaluation of the August 19, 2013, submission containing CMC information, FDA had determined that an exception to the USP Salt Policy was not justified and that the appropriate name for the product designated MM-398 was “Irinotecan Liposome Injection”.

January 19, 2014: FDA issued a “Conditionally Acceptable” letter for the proposed proprietary name, Onivyde.

On August 1, 2014, a general advice meeting was held to seek FDA’s general guidance on the regulatory, preclinical, clinical pharmacology, and statistical contents of the planned NDA. Key discussion items were:

- FDA stated that the major issue regarding the approvability of an NDA that relies on the NAPOLI trial as the single trial supporting efficacy is that the study design is flawed in that it used different 5-fluorouracil regimens in the combination (experimental) and control arms as well as the addition of MM-398 to the combination arm. Introduction of two variables between the experimental and control arms complicates the Agency’s ability to conclude that the OS effect can be attributed to MM-398. In the application, Merrimack should provide a scientific argument as to why the differences between the control and MM-398 combination arms are attributable to the addition MM-398 rather than the differences in chemotherapy regimens. Furthermore, this issue may require discussion with the Oncologic Drugs Advisory Committee (ODAC) or Special Government Employee (SGE) consultants, prior to taking action on the application.
- Merrimack confirmed that the planned NDA would be submitted under the provisions of 505(b)(2), relying on the FDA’s prior findings of safety and effectiveness for irinotecan hydrochloride.
-  (b) (4)
- FDA confirmed that based on the prior orphan drug designation, the irinotecan liposome would be exempt from the requirements of PREA for the proposed indication;
- FDA advised that the results from the NAPOLI-1 trial would be unlikely to support a request for Breakthrough Therapy designation but that a request for Fast Track designation may be appropriate and necessary to support a request for a rolling NDA submission;

- FDA advised that consideration for expanded access should be dictated by the potential demand for such access (i.e., either as single patient INDs or treatment protocol);
- FDA clarified that the CMC pre-NDA meeting should be held before the interdisciplinary pre-NDA meeting in order to capture all of the agreements for the proposed NDA to be reviewed under the PDUFA V program;
- FDA stated that, based on the limited information provided, it does not appear that a risk evaluation and mitigation strategy will be necessary in order to file the NDA.
- FDA stated that the nonclinical data package appeared sufficient to support filing of an NDA and provided additional advice on clinical pharmacology studies (beyond population PK analyses and E-R analyses) that would be required to support a planned NDA based on the approval pathway under 505(b)(2). In particular, an , including studies characterizing *in vivo* stability of the liposome; development of validated bioanalytical method capable of measuring both encapsulated and unencapsulated MM-398; inclusion of the effect of body size on PK, assessment of hepatic impairment on the PK of irinotecan liposome and on SN-38; FDA agreed that Merrimack could rely on FDA's prior findings for irinotecan HCl, specifically labeling regarding drug interactions, renal impairment, distribution, and metabolism, for irinotecan liposome. FDA did not agree with inclusion of results from (b) (4) study in the proposed irinotecan liposome labeling, as the data were considered exploratory only.

September 18, 2014: a preNDA CMC meeting was held to reach agreement on the content of this Quality information in the planned NDA. FDA advised that

- The pharmaceutical development section should provide the packaging qualification study reports including the extractables and leachables studies for the proposed primary packaging components.
- Merrimack should clarify whether a single drug substance supplier or two suppliers will be proposed, competed method validation reports with supporting information for all analytical methods should be provided in the NDA. Summaries are not sufficient.
- In vitro release method should include, but not limited to, the following information: a detailed description of the in vitro release method being proposed for the evaluation of the product and development parameters (selection of the equipment/apparatus, in vitro release media, agitation, pH, sink condition, liposomal integrity, biorelevance, etc.) used to select the proposed in vitro release method as the optimal method for your product.
- The NDA should describe any discriminating ability of the in vitro release method with respect to (b) (4) of the liposome. The testing conditions used for each test should be clearly specified. The release profile should be complete and cover at least (b) (4)% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. The NDA should contain complete in-vitro release profile data, data to support the discriminating ability of the selected in vitro release method, and data to support the discriminating ability of the selected in vitro release method
- The NDA should include a historical summary of changes in (b) (4) and their suppliers; manufacturing process and controls; release specifications; and analytical

methods. Major changes in the formulation (between the clinical and the to-be-marketed products) will require an in-vivo bioequivalence study.

- Specification should characterize the identity and assay for each component of in the liposomes and the NDA should include an explanation as to how the proposed specification provides that information. Merrimack agreed to provide data indicated that the empty liposome do not pose a safety risk.
- FDA stated that the initial shelf life will be based on the data from the primary stability studies on commercial drug product. The proposal to qualify a second drug substance supplier [REDACTED] (b) (4) would be considered if the NDA is able to establish that the materials are chemically equivalent.

November 17, 2014: FDA granted fast track designation for the investigation of irinotecan liposome, in combination with 5-fluorouracil and leucovorin, for the treatment of metastatic adenocarcinoma of the pancreas in patients previously treated with gemcitabine, to demonstrate an improvement in overall survival.

December 2, 2014: FDA held a multidisciplinary preNDA meeting to reach agreement on the content and format of the planned NDA under the PDUFA V program. Key discussion items and agreements reached were:

- The proposed drug product established name (irinotecan liposome injection) appeared acceptable.
- FDA stated that the proposal to submit stability data [REDACTED] (b) (4) was not acceptable; any updated stability data should be provided within 30 days of the final component of the rolling NDA.
- FDA confirmed that the freebase concentration should be cited on the carton/container labeling and in sections 3 and 11 in the package insert in accordance with FDA's salt policy. FDA requested Merrimack refer to the Guidance for Industry: Naming of Drug Products Containing Drug Substance Salt, 2013 at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm379753.pdf>.
- FDA stated that based on the limited safety information provided, a REMS would not be required to file the NDA
- FDA had no objections to Merrimack's proposed approach to address potential impacts of the different 5-FU dosing regimens across the study arms of NAPOLI-1. The proposed approach included submission of published literature supporting the conclusion that 5-FU dose intensities and regimens did not have an effect on OS, data intended to demonstrate that the planned cumulative doses of 5-FU in the 5-FU/LV control arm of NAPOLI-1 were higher than in the MM-398/5-FU/LV arm over a 6-week cycle, and PK simulation results intended to show that the 5-FU area under the curve (AUC) in the 5-FU/LV control arm was higher than in the MM-398/5-FU/LV arm. FDA advised Merrimack to provide justification for the studies selected for assessment of impact of FU dosing regimens on survival, including how the studies were relevant to the proposed indication being sought.
- FDA agreed that the proposal to provide a clinical study report for a single efficacy trial (NAPOLI-1) and to provide clinical study reports with limited patient level data from seven studies as outlined in table 1 of the briefing package, in addition to

complete safety information from the NAPOLI -1 trial, was acceptable. Merrimack should also include all information available to Merrimack that would reasonably affect the Contraindications, Warnings and Precautions, or Adverse Reactions sections of the product label from any investigator-sponsored studies of MM- 398 not described on pages 11-13 of the briefing package or that are listed but not for inclusion in the NDA.

- FDA agreed with the content of the ISS but noted that the database was relatively small (able to detect adverse reactions only at an incidence of $\geq 2\%$).
- FDA agreed that an updated analysis of overall survival, which was event-driven, could be included in the 90-day safety update.

December 23, 2014: FDA granted approval for the rolling review submission schedule for NDA 207793.

History of Regulatory Submission

December 26, 2014: Non-clinical module submitted

March 31, 2015: Chemistry, manufacturing, and controls module submitted

April 24, 2015: Remaining modules submitted.

July 23, 2015: Receipt of 90-day safety update.

3. Chemistry, Manufacturing, and Controls/ Biopharmaceutics/Microbiology

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. As noted in the quality review, irinotecan liposome is a high-risk product based on its formulation in liposomes and its manufacturing methods. Therefore additional data will be supplied post-approval with regard to product characterization as manufacturing experience is gained. Validation of testing is ongoing at this time but does not preclude approval. Manufacturing site inspections were acceptable for sites inspected (e.g., drug substance manufacturing site) as needed or were waived based on inspectional history (e.g., drug product manufacturing site). As noted in the Stability testing supports an expiry of 21 months when stored at 2-8°C, protected from light. There are no outstanding issues that preclude approval.

The labeling of product strength based on irinotecan free base was required under the USP salt policy. Under the USP's policy, USP requires that for drug products that contain a salt, the name of such a drug product usually be expressed only in terms of the active moiety of that drug product, rather than in terms of the salt form. The dosing of irinotecan liposome in the clinical development program utilized strengths and doses according the amount of irinotecan hydrochloride. Both the Quality Review team, the DMEPA consultant, and the clinical review team considered whether expressing the drug name and strength based on the active moiety ("free base") could lead to medication errors based on prior knowledge of the trial or

confusion with the reference listed drug. Based on difference in dose and indication, the FDA staff concluded that the risks of such errors were minimal. Thus, the strength of the vial product of 50 mg/10 mL (5 mg/mL concentration) based on irinotecan hydrochloride was approved as 43 mg/mL (4.3 mg/mL) in the product labeling. Recommended dose based on irinotecan hydrochloride was rounded to the nearest 5 mg for irinotecan free base (e.g., 80 mg/m² irinotecan HCl corresponded to 68.8 mg/m² irinotecan free base, which was rounded up to 70 mg/m²). The exception to this approach was the second dose reduction in patients receiving full strength which was specified as 43 mg irinotecan free base/m² in product labeling. Throughout this Summary Review, the doses of irinotecan liposome are expressed as the free base rather than the salt (irinotecan hydrochloride trihydrate).

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the non-clinical pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

The NDA relied on FDA's prior findings of safety and effectiveness for the following nonclinical studies: nonclinical genotoxicity, nonclinical carcinogenicity, and nonclinical reproductive and developmental toxicity.

In addition, the NDA contained nonclinical pharmacology studies to support proposed labeling claims with regard to mechanism of action and repeat-dose toxicology studies in rats and beagle dogs. Increased exposure and prolonged half-life of irinotecan and SN-38 occurred following irinotecan liposome administration compared to irinotecan HCl in both rats and dogs, with increased clearance observed with irinotecan HCl. The toxicology studies demonstrated effects in multiple organs, with consistent effects in the gastrointestinal tract and bone marrow in both species. There was evidence of neurologic toxicity in the rat. There were no cardiovascular effects observed in beagle dogs.

Non-clinical bridging data were provided in the NDA between irinotecan HCl and irinotecan liposome in nonclinical studies to support the scientific validity of Merrimack's reliance on FDA's prior findings of safety and effectiveness for irinotecan HCl. Onivyde product labeling sections describing nonclinical study results provides the product strength for irinotecan liposome based on the salt (irinotecan hydrochloride trihydrate) for ease of comparison to irinotecan HCl.

5. Clinical Pharmacology/Pharmacogenomics

I concur with the conclusions reached by the clinical pharmacology/pharmacogenomics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

Merrimack relied on FDA's prior findings of safety and effectiveness for irinotecan hydrochloride for drug interactions for irinotecan and its major active metabolite, SN-38, for

labeling with regard to pediatric patients, for those with renal impairment, and for overdosage information.

The NDA contained pharmacokinetic data from 6 clinical trials, including NAPOLI-1, that were evaluated in a population pharmacokinetics (popPK) analysis and in exploratory analyses of exposure-response (NAPOLI-1 only) and exposure-toxicity (all studies). Based on PK analyses of irinotecan liposome, 95% of irinotecan remains liposome-encapsulated for up to 169.5 hours post-dose. In Study PEP205, there were direct comparisons of the PK of irinotecan liposome 100 mg/m² every three weeks with irinotecan HCl 300 mg/m² every 3 weeks. Compared to irinotecan HCl, irinotecan liposome resulted in higher exposure of total irinotecan (C_{max} 13.4-fold, $t_{1/2}$ 2.0-fold, and AUC_{0-inf} 46.2-fold). The formation of SN-38 from irinotecan liposome and of SN-38G from SN-38 after infusion of irinotecan liposome than after irinotecan HCl. The conversion ratios from irinotecan to SN-38 were 0.000289 and 0.0150 and from SN-38 to SN-38G were 11.5 and 16.4 after infusion of irinotecan liposome and irinotecan HCl, respectively.

The popPK analysis did not identify any intrinsic or extrinsic factors requiring dose adjustment; as a result, no recommended dose adjustments based on age, gender, ethnicity (Asian vs. White) or renal impairment was included in product labeling. In addition, these studies indicated that the pharmacokinetics of total irinotecan and total SN-38 were not altered by the co-administration with fluorouracil and leucovorin. Exploratory E-R analyses suggested a correlation between an increase in overall survival (OS) with increase in SN-38 exposure and an increase in grade 3 or 4 neutropenia with increasing SN-38 exposure and in grade 3 or 4 diarrhea with increasing total irinotecan exposure.

The major efficacy study (NAPOLI) required dose adjustments in patients homozygous for UGT1A1*28 allele, due to expected differences in irinotecan and SN-38 metabolism based on the reference listed drug. The experience is limited to 7 patients, in whom use of the lower initial starting dose was tolerated in 6 of the 7 patients (one required dose reduction). While the protocol allowed for escalation if the initial dose was tolerated, there was insufficient numbers of patients to determine how often such dose adjustments are tolerable.

Similarly, the NAPOLI trial excluded patients with elevated serum bilirubin levels, in part based on the labeling for the reference listed drug which notes that there is no recommended dose of irinotecan HCl for patients with bilirubin > 2 mg/dL and that there is an increased risk of Grade 3 -4 neutropenia in patients with serum bilirubin > 1 mg/dL. There were 6 patients enrolled in NAPOLI with baseline bilirubin levels between 1.0 and 2.0 mg/dL; average steady state concentrations for total SN-38 that were increased by 45% compared to patients with baseline bilirubin concentrations of <1.0 mg/dL. These data were insufficient to provide a recommendation for an irinotecan liposome dose for patients with bilirubin levels above 1 mg/dL.

Although the QT IRT consult review stated that “There is no adequate assessment of irinotecan on QT prolongation. A PMR should be requested according to the ICH E14 guidance.” The QT IRT also provided consult review also provided comments on an ongoing pilot study which will obtain information on effects of irinotecan liposome, administered at the

proposed recommended dosage regimen. The clinical pharmacology reviewer did not require a post-marketing requirement (PMR) under 505(o) to evaluate the effects of irinotecan liposome on cardiac electrophysiology based on FDA's prior findings of safety and effectiveness for the reference listed drug, Camptosar, for which safety signals of effects on cardiac electrophysiology have not been identified and where such studies have not been required. In addition, there was no evidence of a safety signal for effects on cardiac electrophysiology in a nonclinical safety pharmacology study or in a repeat dose toxicology study in beagle dogs exposed to irinotecan liposome. Finally, there was no evidence of effects on cardiac electrophysiology on ECGs obtained at baseline and post-treatment in patients enrolled in the NAPOLI-1 trial.

6. Clinical Microbiology

Not applicable. Microbiology sterility issues are discussed under Section 3 of this Summary Review.

7. Clinical/Statistical-Efficacy

The NDA relied on a single, adequately designed and well-controlled trial (see discussion of adequacy of control arm treatment), in which statistically significant and clinically important improvement in overall survival was supported by the consistency of this finding in exploratory analyses of relevant subgroups and by the demonstration of nominally significant improvements in the key secondary efficacy endpoint of progression-free survival and an higher, albeit not clinically important, increase in overall response rate.

Five clinical sites were chosen for inspection by FDA. These sites were selected for inspection using CDER's Clinical Site Selection Tool (CSST). The CSST uses site specific data (e.g., enrollment, adverse event 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. Based on clinical bioresearch monitoring inspections by FDA, the data provided in the NDA were considered reliable.

Key amendments

- The protocol was designed as a two-arm trial comparing overall survival in patients with previously treated pancreatic cancer. Patients were to be randomized to Onivyde or to FU/LV. One interim analysis for futility was to be conducted by an independent monitoring committee.
- On April 9, 2012, the protocol was revised to remove the analysis for futility.
- On June 14, 2012, after enrollment of 63 patients (33 to irinotecan liposome and 30 to FU/LV), the protocol was amended as follows
 - Revision of the protocol title to "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”

- Increase in the sample size from 270 to 450 and increase in the number of events for the final analysis of survival to 305 deaths.
- Addition of a third treatment arm, consisting of irinotecan liposome 70 mg/m² intravenously 5-fluorouracil 2400mg/m² intravenous infusion over 46 hours, and racemic leucovorin 400 mg/m² intravenously every 14 days (2 weeks).
- The statistical plan (SAP) was also revised to describe two pairwise comparisons between Arm A and Arm B and between Arm C and Arm B.
- On October 19, 2012, an amendment was submitted clarifying that:
 - All patients enrolled in the study, regardless of the protocol version, would be included in the planned enrollment of 405 patients
 - Comparison of efficacy between the Arms A and B would include all patients enrolled whereas each comparison of efficacy between Arms C and B would include only those patients in Arm B enrolled on or after the activation of the June 14, 2012, version of the protocol.

Study Design – Final Protocol

Protocol Title: NAPOLI: “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”

Objectives

The primary endpoint was overall survival (OS) with two pair-wise comparisons: irinotecan liposome (Arm A) vs. fluorouracil and leucovorin (FU/LV: Arm B) and irinotecan liposome plus FU/LV (Arm C) vs. Arm B. Key secondary efficacy endpoints were progression-free survival (PFS) and objective response rate (ORR).

Eligibility criteria

adult (≥ 18 years), histologically confirmed, metastatic pancreatic adenocarcinoma; documented disease progression after gemcitabine or gemcitabine-based therapy for adjuvant treatment or for metastatic disease, measurable disease per RECIST v1.1, Karnofsky Performance Status (KPS) ≥ 70 , serum bilirubin within institution limits of normal, normal ECG, adequate renal and hepatic function; and adequate bone marrow reserve.

Under all version of the protocol, patients were equally allocated to available treatment arms; randomization was stratified by albumin levels (<4.0 g/dL vs. ≥ 4.0 g/dL), KPS (70-80 vs. 90-100) and ethnicity (White vs. Asian vs. other).

Treatment Plan

Patients were randomized (1:1:1) to one of the following treatment arms:

- Arm A: irinotecan liposome 100 mg/m² intravenously every three weeks
- Arm B: 5-fluorouracil (5-FU) 2000mg/m² over 24 hours and racemic leucovorin 200 mg/m² weekly for weeks 1-4 weeks of each 6 week cycle

- Arm C: irinotecan liposome 70 mg/m² intravenously, 5-FU 2400mg/m² intravenously over 46 hours, and racemic leucovorin 400 mg/m² intravenously every two weeks.

Tumor status assessments were conducted at baseline and every 6 weeks thereafter; all patients were followed for survival (for patients who were lost-to-follow-up prior to the data cut-off date, at FDA's request, Merrimack provided data from death indices for inclusion in the survival analyses).

Analysis plan (June 14, 2012 protocol)

The sample size of 405 patients and final analysis at 305 deaths, per the June 2012 version of the protocol, was based on the following assumptions: accrual period of 14 months and median survival times of 4.5 months in Arm A, 3 months in Arm B, and 6 months in Arm C. With a total of 305 deaths, the trial would have 85% power to detect a hazard ratio (HR) of 0.67 for the survival comparison between Arms A and B and 95% power to detect a HR of 0.5 for the survival comparison between Arms C and B at an overall alpha of 0.05, two-sided. A Bonferroni-Holm adjustment was used to control the family-wise Type I error rate. The primary analyses for comparison of OS and of PFS were to be performed using an un-stratified log-rank test, with determination of hazard ratio using Cox regression. The primary analysis for ORR was to be performed using a Fisher's exact test. A sequential testing procedure was planned to control the overall type I error rate at the two-sided 0.05 level for the primary and secondary endpoints. The order of the sequence was: OS, PFS, and ORR.

Results

The NAPOLI trial was a global study that randomized 417 patients with metastatic pancreatic cancer who received prior gemcitabine-based therapy between January 11, 2012, and September 11, 2013. The data cut-off date for protocol analyses was February 14, 2014. A total of 151 patients were randomized to Arm A, 149 patients to Arm B, and 117 patients randomized to Arm C. There were 236 patients randomized to Arms B (n=119) and C (n=117) after the June 14, 2012, amendment to the protocol. Based on the final analysis demonstrating efficacy only for this pairwise comparison, this subgroup constitutes the efficacy population supporting approval. Approximately 40% of the patients in this subgroup were accrued at sites in Europe, 29% at sites in Asia, 16% at sites in the US, and 14% in the rest of the world; this distribution is similar to that of the overall study population..

Of the 417 patients randomized, 19 patients (3 patients randomized to Arm A, 14 patients randomized to Arm B and 2 patients randomized to Arm C) did not receive treatment. This imbalance in patients not receiving assigned treatment, favoring the irinotecan liposome arms, is not considered sufficient to account for the observed results.

Among the 236 patients randomized to Arms C or B after activation of the June 14, 2012, amendment, the median age was 63 years (range 34-81 years), of whom 41% were ≥ 65 years of age; 58% were male; 63% were White, 30% were Asian, and 3% were Black; 45% had a baseline albumin level ≥ 4.0 g/dL; and 53% had baseline KPS of 90-100. All patients had received prior gemcitabine; 46% as a single agent and 54% in combination with other agents. Thirteen percent of patients received gemcitabine only in the neoadjuvant/adjuvant setting only. Fifty-five percent of the primary efficacy subgroup had received one prior line of

chemotherapy for metastatic disease while 33% had received ≥ 2 prior lines of therapy for metastatic disease. The most common sites of metastatic disease were liver (67%), lung (31%), distal nodes (27%), and peritoneum (25%).

The analysis of overall survival was conducted after a total of 301 deaths (128 deaths in Arm A, 115 in Arm B, and 77 deaths in Arm C). For the comparisons of Arms B and C, only the 119 patients enrolled after activation of the June 14, 2012 amendment (referred to by the statistical reviewer as Protocol version 2.1), in whom 86 deaths were observed, were included in the analysis. The primary analysis of survival and the Kaplan-Meier curves for survival in Arms A and B, abstracted from the statistical review, is reproduced below.

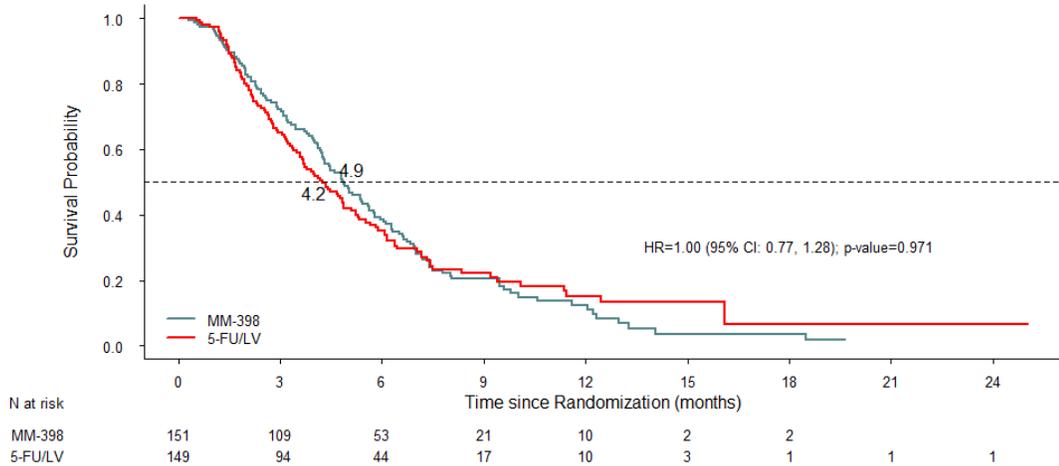
Table 8: Applicant's Overall Survival Results Based on the Amended Dataset with Additional Information (ITT Population)

	All randomized patients in Arms A and B		Randomized patients in Arms C and B under protocol version 2.1 and later	
	MM-398	5-FU/LV	MM-398 + 5-FU/LV	5-FU/LV
Subjects randomized	151	149	117	119
Death	129 (85.4%)	115 (77.2%)	77 (65.8%)	86 (72.3%)
Censored	22 (14.6%)	34 (22.8%)	40 (34.2%)	33 (27.7%)
Overall survival (months) Median (95% CI)	4.9 (4.2, 5.6)	4.2 (3.6, 4.9)	6.1 (4.8, 8.5)	4.2 (3.3, 5.3)
p-value ^a	0.971		0.014	
Hazard ratio (95% CI) ^b	1.00 (0.77, 1.28)		0.68 (0.50, 0.93)	

^a p-value is from an unstratified log-rank test.

^b Hazard ratio is from an unstratified Cox proportional hazards model.

Figure 1: Kaplan-Meier Survival Curves for Overall Survival for Irinotecan liposome (Arm A) vs. Fluorouracil plus Leucovorin (Arm B)

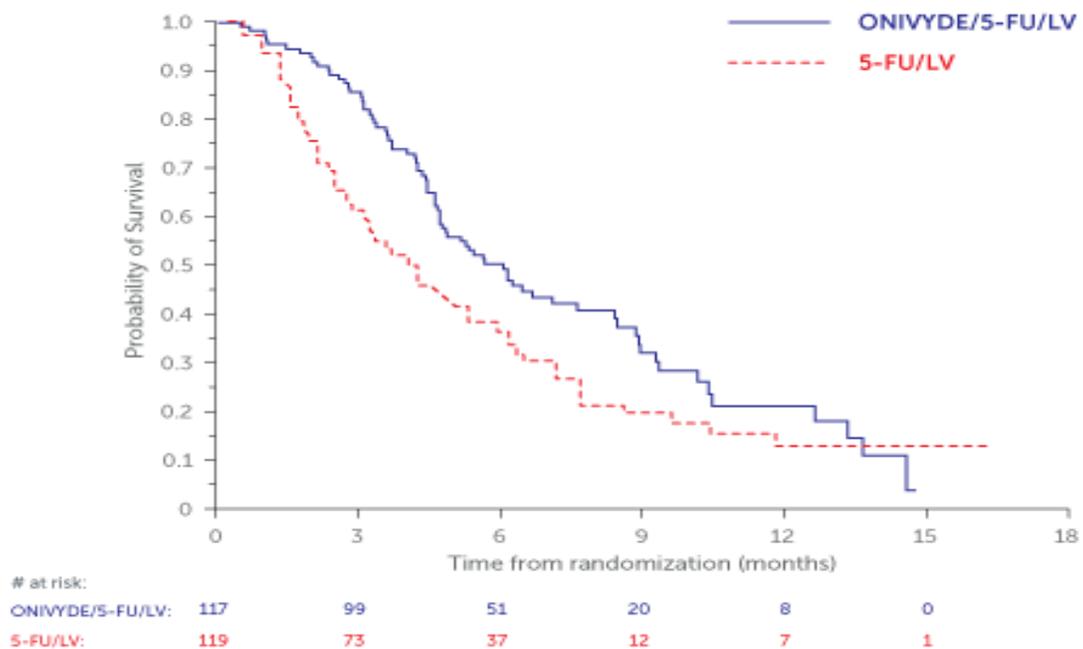


Since the comparison of overall survival for Arms A vs. B was not significantly different, no comparisons of the secondary endpoints were conducted for Arms A vs. B. The pairwise comparison of overall survival between patients randomized to the irinotecan liposome plus FU/LV (Arm C) and the FU/LV (Arm B) was statistically significant, therefore analysis of the key secondary endpoints were performed. As noted by the statistically reviewer, p-values were not included in product labeling because of concerns regarding control of Type 1 error, since the primary analysis of overall survival was not significant for both pairwise comparisons. The results supporting approval for the comparison of the irinotecan liposome combination arm as compared to FU/LV alone are summarized below (abstracted from product labeling).

Efficacy Results for Irinotecan Liposome (ONIVYDE), Fluorouracil, and Leucovorin (Arm C) vs. Fluorouracil plus Leucovorin (Arm B)		
	ONIVYDE/5-FU/LV (N=117)	5-FU/LV (N=119)
Overall Survival		
Number of Deaths, n (%)	77 (66)	86 (72)
Median Overall Survival (months) (95% CI)	6.1 (4.8, 8.5)	4.2 (3.3, 5.3)
Hazard Ratio (95% CI)	0.68 (0.50, 0.93)	
p-value (log-rank test)	0.014	
Progression-Free Survival		
Death or Progression, n (%)	83 (71)	94 (79)
Median Progression-Free Survival (months) (95% CI)	3.1 (2.7, 4.2)	1.5 (1.4, 1.8)
Hazard Ratio (95% CI)	0.55 (0.41, 0.75)	
Objective Response Rate		
Confirmed Complete or Partial Response n (%)	9 (7.7%)	1 (0.8%)

† 5-FU/LV=5-fluorouracil/leucovorin; CI=confidence interval

Figure 2: Kaplan-Meier Survival Curves for Overall Survival for Irinotecan liposome, Fluorouracil, and Leucovorin (Arm C) vs. Fluorouracil plus Leucovorin (Arm B)



As noted in the pre-submission regulatory history, FDA expressed concerns regarding the differences between the FU/LV regimens utilized in Arms B and C. Merrimack provided justification that these differences could not account for the treatment effects, including the absence of data supporting differences in survival based on FU/LV regimen or dose intensity in pancreatic cancer or in colon cancer, a cancer with more extensive studies able to address this issue. In addition, Merrimack noted that the cumulative of fluorouracil was greater in Arm B than Arm C, which would bias against the treatment arm and for the control. FDA sought the advice of two disease experts as SGE consultants (see Section 10 of this Summary Review), who concurred with the justification provided and agreed that the observed results were not likely to be based on differences in the FU/LV dosing between treatment arms.

8. Safety

Size of the database

The safety database is less than that recommended by ICH guidances (300-600 patients) however it is adequate to identify adverse reactions occurring at an incidence of $\geq 2\%$, is supported by FDA's prior findings of safety and effectiveness for the reference listed product (irinotecan HCl) and therefore is considered sufficient to conduct a risk-benefit assessment in this serious and life-threatening disease. The toxicity of irinotecan liposome relied primary on data obtained in 264 patients with previously treated pancreatic cancer in a multicenter, randomized, active-controlled, open-label trial employing two different dosage regimens, where all adverse events were obtained. Specifically, the data were obtained in 147 patients who received at least one dose of irinotecan liposome as a single agent (irinotecan liposome 100 mg/m² as an IV infusion every 3 weeks) and 117 patients who received at least one dose of irinotecan liposome in combination with 5-fluorouracil and leucovorin (irinotecan liposome 70 mg/m² in combination with fluorouracil 2400 mg/m² and leucovorin 400 mg/m² every two weeks). The median exposure to irinotecan liposome in both treatment regimens was 9 weeks. In addition, data on serious adverse reactions (i.e., resulting in hospitalization or death) were identified from 148 additional patients across seven dose-finding or activity-estimating trials of irinotecan liposome.

Adverse reactions led to permanent discontinuation of irinotecan liposome in 11% of patients, to dose reductions of irinotecan liposome in 33% of patients, and to dose delays of irinotecan liposome in 62% of patients receiving of irinotecan liposome in combination with 5-FU/LV. The most common adverse reactions ($\geq 20\%$) of O of irinotecan liposome were diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common, severe laboratory abnormalities ($\geq 10\%$ Grade 3 or 4) were lymphopenia and neutropenia. The most common serious adverse reactions ($\geq 2\%$) of irinotecan liposome were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

Major safety concerns related to labeling

The following adverse reactions of irinotecan liposome were included in a Boxed Warning, Contraindications, and/or Warnings and Precautions sections of the Onivyde product labeling,

- **Severe Neutropenia:** The incidence of fatal neutropenic sepsis of 0.8% among patients receiving irinotecan alone or in combination with fluorouracil and leucovorin. The incidence of Grade 3 or 4 neutropenia (20% vs. 2%) and of Grade 3 or 4 neutropenic fever/neutropenic sepsis (3% vs none) were also higher in patients receiving irinotecan liposome with 5-FU and leucovorin (FU/LV) compared to patients receiving 5-FU/LV alone. The incidence of Grade 3 or 4 neutropenia was higher (55% vs. 18%) among Asian patients (n=33) compared to White patients (n=73) as was the incidence of neutropenic fever/neutropenic sepsis (6% vs. 1%). Based on the serious risks, including fatality due to neutropenic sepsis, product labeling for Onivyde carries a Boxed Warning and Warning for this serious risk. It is noted that product labeling for Camptosar also carries a Boxed Warning for this serious risk.
- **Severe Diarrhea:** Irinotecan liposome should not be administered to patients with bowel obstruction. Severe or life-threatening diarrhea followed one of two patterns: late onset diarrhea (onset more than 24 hours following chemotherapy) and early onset diarrhea (onset within 24 hours of chemotherapy, sometimes occurring with other symptoms of cholinergic reaction). An individual patient may experience both early and late-onset diarrhea.

In the NAPOLI trial, the incidences of Grade 3 or 4 diarrhea at any time (13% vs. 4%), of Grade 3 or 4 late onset diarrhea (9% vs. 4%), and of Grade 3 or 4 early onset diarrhea (3% vs. none) were higher in patients receiving irinotecan liposome with FU/LV compared to those receiving 5-FU/LV. In this trial, 34% irinotecan liposome with FU/LV required loperamide for late-onset diarrhea and 26% required atropine for early-onset diarrhea.

Based on the serious risks of diarrhea, the need to administer additional medications to mitigate this risk, and the need for dose modification (dose reductions or delays), product labeling for Onivyde carries a Boxed Warning and Warning for this serious risk. It is noted that product labeling for Camptosar also carries a Boxed Warning for this serious risk.

- **Interstitial Lung Disease:** Although not observed in clinical studies of irinotecan liposome, irinotecan hydrochloride can cause severe and fatal interstitial lung disease. Based on this finding, the product labeling for Onivyde contains a Warning for this serious risk. The product labeling for Camptosar does not provide information on the incidence of ILD in patients receiving irinotecan hydrochloride.
- **Severe Hypersensitivity Reactions:** Although not observed in clinical studies of irinotecan liposome, irinotecan hydrochloride can cause severe hypersensitivity reactions. Based on this finding, the product labeling for Onivyde carries a contraindication for use in patients with a history of a severe hypersensitivity reaction to ONIVYDE or irinotecan HCl. Although the clinical reviewer noted that non-serious reports of “allergic reaction” were observed, I disagree with her conclusion that these data supported the Contraindication. These findings, alone, were not have been sufficient to support a finding for contraindication of the product as there was no evidence that the risks in patients with less severe reactions outweigh any potential for benefit. The product labeling for Camptosar

does not provide information on the incidence of severe hypersensitivity in patients receiving irinotecan hydrochloride.

- Embryofetal Toxicity: No reproductive toxicology studies were performed for with irinotecan liposome and the proposed labeling is based on the mechanism of action of irinotecan. The DPMH consultant conducted a review of reported cases of pregnancy in patients receiving irinotecan and concluded that “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.”

REMS

I concur with the recommendations of the clinical review team that risk evaluation and mitigation strategies (REMS) are not required to ensure safe and effective use of irinotecan liposome in the indication population.

PMRs and PMCs

The clinical review team did not identify any post-marketing requirements under 505(o) to further investigate serious safety risks or identify areas where post-marketing studies should be requested to further investigate the risks of irinotecan liposome. No other discipline identified the need for PMRs under 505(o) to assess for serious risks.

9. Advisory Committee Meeting

This NDA seeks approval under the provisions of 505(b)(2) for irinotecan liposome, which relies on FDA’s finding of safety and effectiveness for the active pharmaceutical ingredient, irinotecan, approved under NDA The application was not referred to the Oncologic Drugs Advisory Committee (ODAC) because this was not the first drug in this class, the risks of irinotecan liposome were acceptable in the proposed indication, and with the exception of the acceptability of the control arm, the trial design was acceptable. The clinical review team independently consulted two Special Government Employee expert consults, who were experts in the treatment of gastrointestinal malignancies and had served as members of the ODAC in the past. Each consultant independently confirmed that the differences in fluorouracil and leucovorin dosing between the control and Onivyde-containing combination chemotherapy arms was highly unlikely to be able to account for the differences observed in overall survival between the treatment arms, particularly in light of Merrimack’s analysis showing higher cumulative doses of fluorouracil in the control arm .

10. Pediatrics

July 21, 2011: FDA granted orphan drug designation for irinotecan liposome for the treatment of pancreatic cancer on July 21, 2011. Therefore, irinotecan liposome is exempt from the requirements for the Pediatric Research Equity Act (PREA) for this indication.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: An evaluation of the proposed proprietary name for medication errors was conducted by DMEPA on August 8, 2013 (IND 102799), July 17, 2015, (NDA 207793) and again on October 20, 2015. All assessments concluded that the proposed name was acceptable; both the Division of Oncology Product 2 and the Office of Prescription Drug Promotion concurred with these conclusions. The second review during the NDA was to assess whether drug error issues would arise through description of product strength and recommended dose based on the irinotecan free-base rather than irinotecan hydrochloride, as used during the clinical trial (b) (4)
- Physician labeling
 - Boxed Warning: Edited to include information on the incidence of severe neutropenia and severe diarrhea and to succinctly describe recommended actions to be taken with regard to irinotecan liposome administration and medications for management of diarrhea.
 - Indications and Usage: Revised to include a limitation of use stating that Onivyde is not indicated as a single agent for the treatment of metastatic pancreatic cancer.
 - Dosage and Administration: Recommended doses converted to reflect strength of product as irinotecan free-base (b) (4) edited for brevity, legibility, and essential information; removed (b) (4) which was replaced with a statement that there is no recommended dose in patients with elevated bilirubin; streamlined; provide a reference to OSHA website for procedures on handling of genotoxic agents. Removed recommendations regarding (b) (4) which are not supported by clinical experience with this product.
 - Dosage Forms and Strengths: Modified to reflect strength based on irinotecan free base (b) (4) edited for brevity.
 - Contraindications: Edited for brevity
 - Warnings and Precautions: Removed proposed subsection regarding (b) (4) . Removed subsection titled (b) (4)

- (b) (4)
- Removed “ (b) (4) from subsection on Diarrhea; this subsection was revised to describe the risks of severe diarrhea occurring early (due to cholinergic reactions) or late. Edited to provide more information on risks, specifically incidence of risks; removed recommendations not supported by data or vague suggestions (e.g., (b) (4)). Retitled specific warnings to provide explicit information in risks (e.g., ILD, Embryofetal Toxicity). Revised Embryofetal Toxicity subsection for conformance with the Pregnancy and Lactation Labeling Rule (PLLR).
- Adverse Reactions: Revised to provide proportion of patients requiring dose modifications or dose delays; edited tabular listing of adverse reactions by removing (b) (4). Removed subsection (b) (4) on (b) (4). Added subsection providing details on cholinergic reactions other than early onset diarrhea, which were generally not severe or serious. Deleted (b) (4).
 - Drug Interactions: Edited for brevity and essential information
 - Use in Specific Populations: Reformatted for consistency with PLLR. Edited Geriatric Use subsection for conformance with 21 CFR 201.57.
 - Overdosage: Edited for brevity and essential information
 - Description: Removed (b) (4) and edited for brevity.
 - Clinical Pharmacology: Edited section 12.1 to remove (b) (4) and (b) (4) remove description of (b) (4) and (b) (4). Section 12.2 deleted as this is not essential for safe use. Section 12.3 edited for brevity and essential information. Section 12.5 added to provide description of PK in patients homozygous for UGT1A1*28.
 - Nonclinical Pharmacology: Edited for brevity and essential information.
 - Clinical Studies: All doses in the NAPOLI trial described based on irinotecan free base; removed (b) (4). Removed (b) (4). Removed (b) (4) retained KM curve for primary (b) (4) endpoint of OS. Removed (b) (4).
 - References: Added section 15 and included reference to OSHA website, since irinotecan liposome is genotoxic.
 - How Supplied/Storage and Handling: Added reference (to OSHA website).
 - Patient Counseling: Edited in accordance with current labeling practices.

- Carton and immediate container labels: The proposed full prescribing information and immediate carton/container labeling contained statements (DO NOT SUBSTITUTE ONIVYDE for or (b) (4) irinotecan.” “LIPOSOMAL FORMULATION (b) (4)”) similar to those used for doxorubicin liposome injection , in order to mitigate the risks of inadvertent overdose. The DMEPA reviewer requested, and Merrimack revised carton/container labeling to include, addition changes to increase prominence of important information on strength, storage and handling. Final carton/container labeling was deemed acceptable.
- Patient labeling/Medication guide: Merrimack did not propose patient labeling; the clinical review team and consultants did not recommend that patient labeling, specifically a Medication Guide, be developed to ensure safe and effective use.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval
- Risk Benefit Assessment
Approximately half (53%) of all newly diagnosed patients with pancreatic adenocarcinoma have metastatic disease at diagnosis; the 5-year survival rates for patients with metastatic disease is 2.4%. While there are several drugs approved for initial treatment, current recommendations by the NCCN for patients who progress following first-line gemcitabine-based chemotherapy are recommends enrollment in a clinical trial or treatment with fluoropyrimidine-based chemotherapy.

In the NAPOLI trial, the addition of irinotecan liposome to fluoropyrimidine-based chemotherapy, resulting in a statistically significant and clinically important increase in overall survival [HR 0.68 (95% CI: 0.50, 0.93), p=0.014, log-rank test], with median survival times of 6.1 months and 4.2 months, in the irinotecan liposome/FU/LV arm and FU/LV arm, respectively. This finding was consistent within relevant subgroups and supported by evidence of a significant improvement in progression-free survival [HR 0.55 (95% CI: 0.41, 0.75)], with median PFS of 3.1 and 1.5 months, respectively.

These benefits are viewed in the context of the serious risks of neutropenic fever or sepsis and severe diarrhea, and the potential risks of interstitial lung disease and severe hypersensitivity reactions that occur with the reference listed drug. The most common adverse drug reactions were diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common severe (Grade 3-4) laboratory abnormalities were lymphopenia, and neutropenia. The most frequent adverse reactions resulting in discontinuation of irinotecan liposome (occurring in 11% of patients in the irinotecan liposome/FU/LV arm) were diarrhea, vomiting, and sepsis. The most frequent adverse reactions leading to dose reductions (occurring in 33% of patients in the irinotecan liposome/FU/LV arm) or delays (occurring in 62% of patients in the irinotecan liposome/FU/LV arm) were neutropenia, diarrhea, nausea/vomiting, anemia, fatigue, and

thrombocytopenia. These adverse reactions are typical of chemotherapeutic agents, including adverse reactions occurring with gemcitabine-based chemotherapy, which the indicated population will have received. These risks are considered acceptable to the medical and patient community with incurable cancers.

Based on these considerations, the risk-benefit assessment is favorable for approval of irinotecan liposome in the indicated patient population.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**
I concur with the recommendations of the clinical review team that risk evaluation and mitigation strategies (REMS) are not required to ensure safe and effective use of irinotecan liposome in the indication population.
- **Recommendation for other Postmarketing Requirements and Commitments**
The clinical review team did not identify any post-marketing requirements under 505(o) to further investigate serious safety risks or identify areas where post-marketing studies should be requested to further investigate the risks of irinotecan liposome. No other discipline identified the need for PMRs under 505(o) to assess for serious risks.

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/s/

PATRICIA KEEGAN
10/22/2015