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Merrimack Announces ONIVYDE® Regimen Receives Positive CHMP Opinion in European Union

- Positive opinion is based on data from pivotal Phase 3 NAPOLI-1 study
- CHMP recommendation sets path for final review of Shire's marketing authorization application by European Commission
- Shire is responsible for the development and commercialization of ONIVYDE outside of the United States and Taiwan pursuant to an exclusive licensing agreement with Merrimack

CAMBRIDGE, Mass., July 25, 2016 /PRNewswire/ -- Merrimack Pharmaceuticals, Inc. (Nasdaq: MACK) today announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has issued a positive opinion for ONIVYDE® (irinotecan liposome injection), also known as "nal-IRI", in combination with fluorouracil (5-FU) and leucovorin for the treatment of patients with metastatic pancreatic adenocarcinoma who have progressed after gemcitabine-based therapy. The CHMP positive opinion for ONIVYDE will now be reviewed by the European Commission (EC) for marketing authorization. Shire plc (LSE: SHP, NASDAQ: SHPG) is responsible for the development and commercialization of ONIVYDE outside of the United States and Taiwan pursuant to an exclusive licensing agreement with Merrimack.

"This recommendation advances our mission to expand the availability of the ONIVYDE regimen to metastatic pancreatic cancer patients worldwide," said Robert Mulroy, President and CEO of Merrimack. "The CHMP's positive opinion is further validation of the clinical importance of the ONIVYDE regimen. We are grateful to all of the patients, families and investigators who contributed to the development of ONIVYDE, and to our partner Shire, together with whom we are committed to advancing the availability of this important therapy to patients facing this devastating disease with few treatment options."

"This regulatory milestone is an important step for patients with metastatic pancreatic adenocarcinoma who have progressed after gemcitabine-based therapy," said Philip J. Vickers, Ph.D., Head of R&D, Shire. "There has been little improvement in prognosis for patients in this setting for over 20 years, and given this high unmet need we look forward to receiving the final approval decision from the European Commission."

The opinion was based on data from the pivotal Phase 3 NAPOLI-1 study, which demonstrated that ONIVYDE in combination with 5-FU and leucovorin met its primary endpoint of significantly increased overall survival when compared to 5-FU and leucovorin alone: 6.1 months vs 4.2 months (p=0.012, unstratified hazard ratio (HR) =0.67, 95% CI: [0.49-0.92]) [i]. Findings from an updated analysis of the NAPOLI-1 data showed that one in four patients treated with the ONIVYDE combination regimen survived a milestone one year or more: 12-month overall survival estimates of 26% (95% CI, 18-35%) were observed in the ONIVYDE combination treatment arm representing a 63% improvement when compared to 16% (95% CI, 10-24%) for 5-FU and leucovorin alone[ii]. This updated analysis was presented at the American Society of Clinical Oncology 2016 Gastrointestinal Cancers Symposium.

The primary NAPOLI-1 study results were the basis for the October 2015 U.S. Food and Drug Administration (FDA) and Taiwan FDA approvals of the ONIVYDE combination regimen for the treatment of patients with metastatic pancreatic adenocarcinoma whose disease progressed after gemcitabine-based therapy. It is the first and only U.S. FDA-approved therapy in this setting. The ONIVYDE combination is also designated as a category 1 treatment option in the 2016 National Comprehensive Cancer Network (NCCN) guidelines for pancreatic adenocarcinoma in the U.S. as well as a category 2B status in the 2015 European Society for Medical Oncology (ESMO) clinical practice guidelines in the EU.

About Pancreatic Cancer

Pancreatic cancer is a rare and deadly disease with only 7% of all patients surviving five years or longer[iii]. There are approximately 50,000 patients diagnosed with pancreatic cancer each year in the United States[iv], the overwhelming majority of which have adenocarcinoma[v]. Globally there are approximately 338,000 new cases each year[vi]. Most patients receive gemcitabine-based therapy during either adjuvant/neoadjuvant treatment for locally advanced disease or during first- or second-line therapy for metastatic disease[vii], but are left with no standard of care therapy upon progression. ONIVYDE in combination with 5-FU and leucovorin is approved in the United States and Taiwan for these patients whose disease has progressed following gemcitabine-based therapy.

About ONIVYDE® [pronounced ** 'on - ih - vide **\]

ONIVYDE® (irinotecan liposome injection), also known as MM-398 or "nal-IRI," is a novel encapsulation of irinotecan in a liposomal formulation. The activated form of irinotecan is SN-38, which functions by inhibiting topoisomerase I (an essential enzyme involved in DNA transcription and replication) and promoting cell death. ONIVYDE was approved by the U.S. FDA in combination with fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. For full prescribing information, including Boxed WARNING, please visit www.ONIVYDE.com.

IMPORTANT SAFETY INFORMATION - UNITED STATES

INDICATION
ONIVYDE® (irinotecan liposome injection) is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA
Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with fluorouracil (5-FU) and leucovorin (LV). Withhold ONIVYDE for absolute neutrophil count below 1500/mm^3 or neutropenic fever. Monitor blood cell counts periodically during treatment.
Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with 5-FU/LV. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2-4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.

CONTRAINDICATION
ONIVYDE is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE or irinotecan HCl.

WARNINGS AND PRECAUTIONS

Severe Neutropenia
ONIVYDE can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In a clinical study, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE, occurring in 1/117 patients in the ONIVYDE/5-FU/LV arm and 1/147 patients receiving ONIVYDE as a single agent. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE/5-FU/LV vs 2% of patients receiving 5-FU/LV. Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE/5-FU/LV, and did not occur in patients receiving 5-FU/LV.

In patients receiving ONIVYDE/5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian vs 1% of White patients.

Severe Diarrhea
ONIVYDE can cause severe and life-threatening diarrhea. Do not administer ONIVYDE to patients with bowel obstruction. Severe and life-threatening late-onset (onset > 24 hours after chemotherapy) and early-onset diarrhea (onset ≤24 hours after chemotherapy, sometimes with other symptoms of cholinergic reaction) were observed. An individual patient may experience both early- and late-onset diarrhea.

In a clinical study, Grade 3/4 diarrhea occurred in 13% of patients receiving ONIVYDE/5-FU/LV vs 4% receiving 5-FU/LV. Grade 3/4 late-onset diarrhea occurred in 9% of patients receiving ONIVYDE/5-FU/LV vs 4% in patients receiving 5-FU/LV; the incidences of early-onset diarrhea were 3% and no Grade 3/4 incidences, respectively. Of patients receiving ONIVYDE/5-FU/LV, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea.

Interstitial Lung Disease (ILD)
Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD.

Severe Hypersensitivity Reactions
Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction.

Embryo-Fetal 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. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during and for 1 month after ONIVYDE treatment.

ADVERSE REACTIONS

- The most common (≥20%) adverse reactions in which patients receiving ONIVYDE/5-FU/LV experienced a ≥5% higher incidence of any Grade vs the 5-FU/LV arm, were diarrhea (any 59%, 26%; severe 13%, 4%) (early diarrhea [any 30%, 15%; severe 3%, 0%], late diarrhea [any 43%, 17%; severe 9%, 4%]), fatigue/asthenia (any 56%, 43%; severe 21%, 10%), vomiting (any 52%, 26%; severe 11%, 3%), nausea (any 51%, 34%; severe 8%, 4%), decreased appetite (any 44%, 32%; severe 4%, 2%), stomatitis (any 32%, 12%; severe 4%, 1%), pyrexia (any 23%, 11%; severe 2%, 1%).
- Of less common (< 20%) adverse reactions, patients receiving ONIVYDE/5-FU/LV who experienced Grade 3/4 adverse reactions at a ≥2% higher incidence of Grade 3/4 toxicity vs the 5-FU/LV arm, respectively, were sepsis (3%, 1%), neutropenic fever/neutropenic sepsis (3%, 0%), gastroenteritis (3%, 0%), intravenous catheter-related infection (3%, 0%), weight loss (2%, 0%), and dehydration (4%, 2%).
- The laboratory abnormalities in which patients receiving ONIVYDE/5-FU/LV experienced a ≥5% higher incidence vs the 5-FU/LV arm, were anemia (any 97%, 86%; severe 6%, 5%), lymphopenia (any 81%, 75%; severe 27%, 17%), neutropenia (any 52%, 6%; severe 20%, 2%), thrombocytopenia (any 41%, 33%; severe 2%, 0%), increased alanine aminotransferase (any 51%, 37%; severe 6%, 1%), hypoalbuminemia (any 43%, 30%; severe 2%, 0%), hypomagnesemia (any 35%, 21%; severe 0%, 0%), hypokalemia (any 32%, 19%; severe 2%, 2%), hypocalcemia (any 32%, 20%; severe 1%, 0%), hypophosphatemia (any 29%, 18%; severe 4%, 1%), hyponatremia (any 27%, 12%; severe 5%, 3%), increased creatinine (any 18%, 13%; severe 0%, 0%).
- ONIVYDE can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis with abdominal cramping and early-onset diarrhea. Grade 1/2 cholinergic symptoms other than early diarrhea occurred in 12 (4.5%) ONIVYDE-treated patients.
- Infusion reactions, consisting of rash, urticaria, periorbital edema, or pruritus, occurring on the day of ONIVYDE administration were reported in 3% of patients receiving ONIVYDE or ONIVYDE/5-FU/LV.
- The most common serious adverse reactions (≥2%) of ONIVYDE were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

DRUG INTERACTIONS
Avoid the use of strong CYP3A4 inducers, if possible, and substitute non-enzyme-inducing therapies ≥2 weeks prior to initiation of ONIVYDE. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible, and discontinue strong CYP3A4 inhibitors ≥1 week prior to starting therapy.

USE IN SPECIFIC POPULATIONS

Pregnancy and Reproductive Potential
Advise pregnant women of the potential risk to a fetus. Advise males with female partners of reproductive potential to use effective contraception during and for 4 months after ONIVYDE treatment.

Lactation
Advise nursing women not to breastfeed during and for 1 month after ONIVYDE treatment.

Pediatric
Safety and effectiveness of ONIVYDE have not been established in pediatric patients.

DOSAGE AND ADMINISTRATION

The recommended dose of ONIVYDE is 70 mg/m^2 intravenous (IV) infusion over 90 minutes every 2 weeks, administered prior to LV and 5-FU. The recommended starting dose of ONIVYDE in patients known to be homozygous for the UGT1A1*28

allele is 50 mg/m^2 administered by IV infusion over 90 minutes. There is no recommended dose of ONIVYDE for patients with serum bilirubin above the upper limit of normal. Premedicate with a corticosteroid and an anti-emetic 30 minutes prior to ONIVYDE. Withhold ONIVYDE for Grade 3/4 adverse reactions. Resume ONIVYDE with reduced dose once adverse reaction recovered to ≤Grade 1. Discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction and in patients with a confirmed diagnosis of ILD.

Do not substitute ONIVYDE for other drugs containing irinotecan HCl.

Please see full U.S. Prescribing Information **for ONIVYDE.**

Global Partnerships

In 2014, Merrimack and Shire plc entered into an exclusive licensing agreement for the development and commercialization of ONIVYDE outside of the United States and Taiwan. PharmaEngine, Inc. (Taipei, Taiwan) holds the rights to commercialize ONIVYDE in Taiwan and received the Taiwan FDA approval of ONIVYDE in October 2015.

About Merrimack

Merrimack is a fully integrated biopharmaceutical company that views cancer as a complex engineering challenge. Through systems biology, which brings together the fields of biology, computing and engineering, Merrimack aims to decrease uncertainty in drug development and clinical validation, and move discovery efforts beyond trial and error. Such an approach has the potential to make individualized treatment of patients a reality. Merrimack's first commercial product, ONIVYDE® (irinotecan liposome injection), was approved by the U.S. FDA in October 2015. With four additional candidates in clinical studies, several in preclinical development and multiple biomarkers designed to support patient selection, Merrimack is building one of the most robust oncology pipelines in the industry. For more information, please visit Merrimack's website at www.merrimack.com or connect on Twitter at @MerrimackPharma.

Forward-looking Statements

To the extent that statements contained in this press release are not descriptions of historical facts, they are forward-looking statements reflecting the current beliefs and expectations of management made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements include any statements about Merrimack's strategy, future operations, future financial position, future revenues and future expectations and plans and prospects for Merrimack, and any other statements containing the words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions. In this press release, Merrimack's forward-looking statements include, among others, statements about the potential approval of ONIVYDE in the European Union and the potential effectiveness and safety profile of ONIVYDE. Such forward-looking statements involve substantial risks and uncertainties that could cause Merrimack's clinical development programs, future results, performance or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, the uncertainties inherent in the initiation of future clinical trials, availability of data from ongoing clinical trials, expectations for regulatory approvals and other matters that could affect the availability or commercial potential of Merrimack's products, product candidates or companion diagnostics. Merrimack undertakes no obligation to update or revise any forward-looking statements. Forward-looking statements should not be relied upon as representing Merrimack's views as of any date subsequent to the date hereof. For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to Merrimack's business in general, see the "Risk Factors" section of Merrimack's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on May 2, 2016 and other reports Merrimack files with the SEC.

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[i] Wang-Gillam A, et.al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after

previous gemcitabine-based therapy (NAPOLI-1): a global, randomized, open-label phase 3 trial. *The Lancet*. Vol. 387, No. 10018, p545-557, 6 Feb 2016

[ii] Wang-Gillam A, et.al. Updated overall survival analysis of NAPOLI-1: Phase III study of nanoliposomal irinotecan (nal-IRI, MM-398), with or without 5-fluorouracil and leucovorin (5-FU/LV), versus 5-FU/LV in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy. J Clin Oncol 34, 2016 (suppl 4S; abstr 417)

[iii] American Cancer Society. Cancer Facts and Figures 2016. Atlanta: American Cancer Society; 2016

[iv] American Cancer Society. Cancer Facts and Figures 2016. Atlanta: American Cancer Society; 2016

[v] American Cancer Society. Cancer Facts and Figures 2016. Atlanta: American Cancer Society; 2016

[vi] World Health Organization. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012; Lyon, Fr.: International Agency for Research on Cancer; 2012

[vii] Data presented at ASCO 2014 (Abrams et al.)