

## Press Release

### **SHIONOGI AND MOLTENI CONCLUDE A CONTRACT FOR THE COMMERCIALIZATION OF RIZMOIC® (NALDEMEDINE), AN OPIOID-INDUCED CONSTIPATION THERAPEUTIC AGENT IN ITALY AND POLAND**

**AMSTERDAM, Netherlands, and Florence, Italy May 22<sup>st</sup>, 2019** – SHIONOGI B.V., the European subsidiary of SHIONOGI & Co., Ltd. (Head Office: Osaka, Japan; President & CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi") and L. MOLTENI & C. DEI F.LLI ALITTI SOCIETÀ DI ESERCIZIO S.P.A. (Headquarters: Florence, Italy; Managing Director : Giuseppe Seghi Recli, hereafter "Molteni") announced today that Shionogi and Molteni concluded a contract for the distribution and sale of RIZMOIC® (naldemedine) for the treatment of opioid-induced constipation (OIC) in adult patients previously treated with a laxative in the two key European markets, Italy and Poland.

Shionogi has built a strong heritage in research-based medicine. The company's research and development efforts target pain/central nervous system as one of its priority areas in the mid-term business plan. The company constantly strives to improve the quality of life of patients who suffer from pain or side effects of analgesics by bringing forth innovative drugs.

Molteni is a specialty leader in the field of opioid treatments in Europe and is committed to researching and developing novel solutions for the treatment of moderate to severe pain and addiction, to safeguard patients' quality of life and care. According to this contract, Molteni will distribute and sell RIZMOIC® in Italy and Poland and Shionogi will co-promote the product in Italy with Molteni.

Dr. John Keller, Chief Executive Officer of Shionogi B.V., the subsidiary of Shionogi in Europe, said *"This partnership marks another key milestone for the launch of RIZMOIC® in Europe. By partnering with Molteni, we are combining our extensive knowledge of opioid pain management to ensure more patients experiencing OIC can have access to this important treatment option. The co-promotion of Shionogi and Molteni in Italy offers a synergic partnership to maximise the value of existing commercial structures"*.

Molteni's Managing Director, Giuseppe Seghi Recli, commented, "We are delighted to partner with Shionogi on such a promising new molecule for the treatment of OIC and we believe that the outstanding commitment shown by both parties since the beginning of our discussion will significantly contribute to raising a new patient's awareness capable to tackle this disabling and under diagnosed pathology."

On February 22, 2019, the European Commission (EC) granted the Marketing Authorization (MA) for RIZMOIC® for the treatment of OIC in adult patients who have previously been treated with a laxative.<sup>1,2</sup> RIZMOIC® is planned to be launched in Italy and Poland in 2020. RIZMOIC® was launched under the brand name Symproic® in Japan in June 2017, and in the United States in October 2017.<sup>3-5</sup>



Shionogi plans to initiate a clinical study of naldemedine in paediatric patients with OIC in the EU, in accordance with an agreed paediatric investigation plan, as well as a clinical study in adult patients with post-operative ileus.

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### **About Opioid-induced Constipation**

Constipation is one of the most commonly reported side effects associated with opioid treatment, particularly among patients with chronic non-cancer pain and patients with cancer pain.<sup>6</sup> OIC is a result of increased fluid absorption and reduced gastro-intestinal (GI) motility due to mu-opioid receptor binding in the GI tract. OIC is defined as a change in bowel habits that is characterized by any of the following after initiating opioid therapy: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency.<sup>7</sup> In patients receiving opioid therapy for chronic non-cancer pain, the prevalence of OIC ranges from approximately 40-60 percent.<sup>8</sup>

### **About RIZMOIC<sup>®</sup>**

RIZMOIC<sup>®</sup> (naldemedine) is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have previously been treated with a laxative. RIZMOIC<sup>®</sup> is a peripherally acting mu-opioid receptor antagonist (PAMORA) that has been developed by Shionogi as a once-daily treatment of OIC. The efficacy and safety of naldemedine have been evaluated in randomized, double-blinded, placebo-controlled studies in adult patients with OIC who have chronic non-cancer pain or who have cancer pain.<sup>9-13</sup> RIZMOIC<sup>®</sup> is expected to be a new treatment option that can improve the quality of life significantly in patients with OIC in pain management with opioid analgesics.

### **About Shionogi**

Shionogi & Co., Ltd. ("Shionogi") is a Japanese major research-driven pharmaceutical company dedicated to bringing benefits to patients based on its corporate philosophy of "supplying the best possible medicine to protect the health and wellbeing of the patients we serve." The company currently markets products in several therapeutic areas including anti-infectives, pain, CNS disorders and gastroenterology. Shionogi's research and development currently target two therapeutic areas: infectious diseases and pain/CNS disorders. For more information on Shionogi, please visit <http://www.shionogi.co.jp/en/>. Shionogi B.V. is the European subsidiary of Shionogi & Co., Ltd. based in Amsterdam, Netherlands. For more information on Shionogi B.V. please visit <http://www.shionogi.eu/>.

### **About Molteni**

Founded in Florence in 1892, Molteni is a privately-held specialty pharmaceutical company developing, manufacturing and marketing pharmacological treatments for addictions and moderate to severe pain. Molteni is a leader in the field of drug dependence. Molteni operates both directly, in Italy and Poland, and through its network of specialized partners in more than 50 countries and it is a preferred and qualified partner of International Organizations and Non-Governmental Organizations such as UNICEF, UNDP, IDA Foundation and Global Fund. For more information, please visit <http://www.moltenifarma.it/>.

### **Forward Looking Statement**

*This announcement contains forward-looking statements. These statements are based on expectations in light of the information currently available, assumptions that are subject to risks and uncertainties which could cause actual results to differ materially from these statements. Risks and uncertainties include general domestic and international economic conditions such as general industry and market conditions, and changes of interest rate and*

currency exchange rate. These risks and uncertainties particularly apply with respect to product-related forward-looking statements. Product risks and uncertainties include, but are not limited to, completion and discontinuation of clinical trials; obtaining regulatory approvals; claims and concerns about product safety and efficacy; technological advances; adverse outcome of important litigation; domestic and foreign healthcare reforms and changes of laws and regulations. Also for existing products, there are manufacturing and marketing risks, which include, but are not limited to, inability to build production capacity to meet demand, unavailability of raw materials and entry of competitive products. The company disclaims any intention or obligation to update or revise any forward-looking statements whether as a result of new information, future events or otherwise.

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<sup>1</sup> [Release on February 22, 2019](#)

Shionogi announces European Union Marketing Authorisation for RIZMOIC<sup>®</sup> (naldemedine) for the treatment of opioid-induced constipation in adults previously treated with a laxative

<sup>2</sup> SmPC, RIZMOIC<sup>®</sup>, Shionogi, Feb 2019.

<sup>3</sup> [Release on June 7, 2017](#)

Opioid-Induced Constipation therapeutic agent ‘Symproic<sup>®</sup> (naldemedine) Tablets 0.2mg’ launched in Japan

<sup>4</sup> [Release on October 12, 2017](#)

Shionogi Inc. and Purdue Pharma L.P. Announce U.S. Availability of Symproic<sup>®</sup> (naldemedine) for the Treatment of Opioid-Induced Constipation in Adults with Chronic Non-Cancer Pain

<sup>5</sup> [Release on April 11, 2019](#)

Shionogi Announces Licensing of Symproic<sup>®</sup> (naldemedine) to BioDelivery Sciences International Inc.

<sup>6</sup> Sehgal N, et al. Chronic pain treatment with opioid analgesics benefits versus harms of long-term therapy. Expert Rev Neurother. 2013;13:1201-1220.

<sup>7</sup> Camilleri M, et al. Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation. Neurogastroenterol Motil. 2014;26: 1386-1395.

<sup>8</sup> Coyne E, et al. Opioid-Induced constipation among patients with chronic Noncancer pain in the United States, Canada, Germany and the United Kingdom: Laxative use, response and symptom burden over time. Pain. 2015;16:1551–1565.

<sup>9</sup> Hale M, et al. Naldemedine versus placebo for opioid-induced constipation (COMPOSE-1 and COMPOSE-2): two multicentre, phase3, double-blind, randomised, parallel-group trials. Lancet Gastroenterol Hepatol. 2017. Published online May 30, 2017.

<sup>10</sup> Webster L, et al. Long term use of naldemedine in the treatment of opioid-induced constipation in patients with chronic noncancer pain: a randomized, double-blind, placebo-controlled phase 3 study. Pain. 2018. Published online February 6 2018.

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- <sup>12</sup>. Katakami N, et al. Randomized phase III and extension studies: efficacy and impacts on quality of life of naldemedine in subjects with opioid-induced constipation and cancer. *Ann Oncol*. 2018. Published online Apr 18, 2018.
- <sup>13</sup>. Satomi E, et al. Efficacy and tolerability of naldemedine in patient with cancer and opioidinduced constipation: A pooled subgroup analysis of 2 randomised placebo-controlled studies. *Ann Oncol*. 2018. 29 (suppl 8).