

Press Release

SHIONOGI AND FERRER CONCLUDE A CONTRACT FOR THE PROMOTION IN SPAIN OF ▼ RIZMOIC® (NALDEMEDINE), A THERAPEUTIC AGENT FOR OPIOID-INDUCED CONSTIPATION

AMSTERDAM, Netherlands and BARCELONA, Spain, June 19, 2019 – SHIONOGI B.V., the European subsidiary of SHIONOGI & Co., Ltd. (Head Office: Osaka, Japan; President & CEO: Isao Teshirogi, Ph.D.; hereafter "Shionogi") and Ferrer (Headquarters: Barcelona, Spain; CEO: Mario Rovirosa) announced today that Shionogi and Ferrer concluded an exclusive promotion agreement for RIZMOIC® (naldemedine) in Spain for the treatment of opioid-induced constipation (OIC) in adult patients previously treated with a laxative.

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 therapeutic areas of interest. 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.

Ferrer's activity covers the entire health spectrum in Spain and many other countries worldwide, including expertise in pain management by opioid treatment. The company's strong commitment to improving the wellbeing of society and its integrated model spanning from R&D through to distribution, ensures their range of products offer real benefits in rapidly changing environments.

Dr. John Keller, Chief Executive Officer of Shionogi B.V., the subsidiary of Shionogi in Europe, said *"We are delighted to collaborate with Ferrer in Spain. This collaboration marks an additional key milestone for the launch of RIZMOIC® in Europe. Ferrer is a company that is well trusted and highly respected, with not only an established commercial structure that is ideal for the introduction of RIZMOIC®, but also a deep knowledge of pain management that augments and aligns with our own."*

Ferrer's Chief Executive Officer, Mario Rovirosa, commented, *"We are pleased to partner with Shionogi on this promising treatment which has the potential to make a real impact on the lives of many people currently suffering from OIC across Spain. This partnership allows us to introduce an innovative treatment to reduce the burden in this disease area. Moreover, this agreement complements our expertise in the field of pain relief"*.

On February 18, 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.^{1,2} RIZMOIC® is planned to be launched in Spain in 2020. RIZMOIC® was launched under the brand name Symproic® in Japan in June 2017, and in the United States in October 2017.³⁻⁵

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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.⁶ 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.⁷ In patients receiving opioid therapy for chronic non-cancer pain, the prevalence of OIC ranges from approximately 40-60 percent.⁸

About RIZMOIC®

RIZMOIC® (naldemedine) is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have previously been treated with a laxative. RIZMOIC® 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.⁹⁻¹³ RIZMOIC® 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.

▼ This medicinal product is subject to additional monitoring. Detailed information on this medicinal product is available on the website of the European Medicines Agency www.ema.europa.eu.

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, gynaecology 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 www.shionogi.eu.

About Ferrer

Founded in Spain in 1959, Ferrer is a privately-held international pharmaceutical company headquartered in Barcelona. It is active throughout the full value chain, from R&D to international distribution. It is present in more than 110 countries, with 19 international affiliates. Ferrer is active in the pharmaceutical, health, fine chemical and food sectors, key areas for contributing to people's health and wellbeing. Since the beginning, Ferrer has been committed to the research and development of innovative medicinal products and to maintain a solid industrial structure. Ferrer's activity across the entire healthcare spectrum includes prescription drugs, hospital products and diagnostics. For more information on Ferrer, please visit www.ferrer.com.

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.

For further information, contact:

Shionogi Europe

Dr. Mark Hill, Shionogi, mark.hill@shionogi.eu
Mirjam Korn, Shionogi, mirjam.korn@shionogi.eu

Shionogi & Co., Ltd.

Corporate Communications Department
Telephone: +81-6-6209-7885

Ferrer BD and Licensing

Ana Aliaga, Ferrer, aaliaga@ferrer.com

Ferrer Corporate Communications

Gorka Ortiz de Zárate, Ferrer, gortizdezarate@ferrer.com

References

¹ [Release on February 22, 2019](#)

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

² SmPC, RIZMOIC®, Shionogi, Feb 2019. [online] Available at: https://www.ema.europa.eu/documents/product-information/rizmoic-epar-product-information_en.pdf [Accessed 20 May 2019].

³ [Release on June 7, 2017](#)

Opioid-Induced Constipation therapeutic agent 'Symproic®' (naldemedine) Tablets 0.2mg' launched in Japan

⁴ [Release on October 12, 2017](#)

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

⁵ [Release on April 11, 2019](#)

Shionogi Announces Licensing of Symproic® (naldemedine) to BioDelivery Sciences International Inc.

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

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

⁸ 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.

⁹ 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.

¹⁰ 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.

¹¹ Bowers B, et al. The evolving role of long-term pharmacotherapy for opioid-induced constipation in patients being treated for noncancer pain. Jour Pharm Practice. 2017.

¹² 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.

¹³ Satomi E, et al. Efficacy and tolerability of naldemedine in patient with cancer and opioid induced constipation: A pooled subgroup analysis of 2 randomised placebo-controlled studies. Ann Oncol. 2018. 29 (suppl 8).