Press Release

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

- **Today the European Commission (EC) granted a Marketing Authorisation (MA) for Rizmoic® (naldemedine), for the treatment of opioid-induced constipation (OIC) in adult patients who have previously been treated with a laxative**
- **The EC's approval of RIZMOIC is based on data from three Phase 3 efficacy and safety studies (V9231, V9232 and V9236) and one long-term safety study (V9235)**
- **The results of these studies support the efficacy of RIZMOIC, showing treatment with naldemedine was associated with a statistically significant increase in the spontaneous bowel movement (SBM) response rate compared to placebo.**

OSAKA, Japan, and LONDON, UK, 22 February 2019 – Shionogi & Co., Ltd. (hereafter "Shionogi"), a research-driven pharmaceutical company, announced today that the European Commission(EC) has granted Marketing Authorisation(MA) for Rizmoic® (naldemedine), for the treatment of opioid-induced constipation (OIC) in adult patients who have previously been treated with a laxative.

This decision by the EC has followed adoption of the positive opinion of the Committee for Medicinal Products for Human Use (CHMP) in December 2018.

Welcoming the announcement, Dr. John Keller, Chief Executive Officer of Shionogi Ltd, said "Today's EU marketing authorisation for RIZMOIC allows patients with opioid-induced constipation already taking laxatives access to an important new treatment that can relieve their suffering from this much under-recognised condition that can significantly affect their quality of life."

Dr. Viola Andresen, specialist in Internal Medicine at the Israelitic Hospital in Hamburg, Germany, commented
"We as physicians are highly welcoming this announcement, because the peripherally acting μ-opioid antagonist (PAMORA) naldemedine is an effective and well-tolerated therapy for opioid-induced constipation and will therefore add an important value for the therapeutic management of patients suffering from OIC. "

OIC is a prevalent and distressing side effect of opioid therapy that does not reliably respond to treatment with conventional laxatives.[1]

The efficacy and safety of RIZMOIC has been established in 2 replicate 12-week, phase 3, randomised, double-blind, placebo-controlled studies in patients with chronic non-cancer pain and OIC (V9231 and V9232)[2]. A phase 3 long-term (52-week) randomised double-blind, placebo-controlled study in subjects with chronic non-cancer pain and OIC was conducted to evaluate long term safety.[3,4] Efficacy and safety were also established in randomised, double-blind, placebo group, comparator studies in patients with cancer and OIC (V9236).[5,6] The results of these studies support the efficacy of naldemedine, showing treatment with naldemedine was associated with a statistically significant increase in the spontaneous bowel movement (SBM) response rate over 12 weeks compared to placebo (47.6% vs. 34.6%, p=0.002; 52.5% vs. 33.6%, p<0.0001, respectively)[2] in the two studies in patients with non-cancer pain, and a statistically significant increase in the SBM response rate over 2 weeks compared to placebo (71.1% vs 34.4%, p<0.0001) in a study in patients with cancer.[5] The most common side effects are abdominal pain, diarrhoea, nausea, and vomiting.[2]

Naldemedine, which has already been approved for routine use in the US and Japan, is an antagonist of opioid binding at the mu-, delta-, and kappa-opioid receptors. Naldemedine is a derivative of naltrexone to which a side chain has been

added that increases the molecular weight and the polar surface area, thereby reducing its ability to cross the blood-brain barrier (BBB); the CNS penetration of naldemedine is expected to be negligible at the recommended dose. Additionally, naldemedine is a substrate of the P-glycoprotein (P-gp) efflux transporter, which may also be involved in reducing naldemedine penetration into the CNS. Based on this, naldemedine is expected to exert its anti-constipating effects on opioids without reversing their CNS-mediated analgesic effects.

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About Opioid-induced Constipation

Constipation is one of the most commonly reported side effects associated with opioid treatment, including among patients with chronic non-cancer pain and patients with cancer.[7] OIC is a result of increased fluid absorption and reduced 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.[8] In patients receiving opioid therapy for chronic non-cancer pain, the prevalence of OIC ranges from approximately 40-60 percent.[1]

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, cardiovascular diseases 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/.

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.

References:

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