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

OSAKA, Japan, and LONDON, UK, 22nd 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 Limited, 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 naldemedine 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.

ENDS

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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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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Rizmoic 200 micrograms film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 micrograms naldemedine (as tosylate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).
Round, approximately 6.5 mm diameter, yellow tablet debossed with '222' and Shionogi logo on one side and '0.2' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rizmoic is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have previously been treated with a laxative.

4.2 Posology and method of administration

Posology
The recommended dose of naldemedine is 200 micrograms (one tablet) daily.
Rizmoic may be used with or without laxative(s). It may be taken at any time of the day but it is recommended to be taken at the same time every day.
Alteration of the analgesic dosing regimen prior to initiating Rizmoic is not required.
Rizmoic must be discontinued if treatment with the opioid pain medicinal product is discontinued.

Special populations
Elderly patients
No dose adjustment is required in patients older than 65 years of age (see section 5.2).
Due to the limited therapeutic experience in patients 75 years old and older, naldemedine therapy should be initiated with caution in this age group.

Renal impairment
No dose adjustment is required in patients with renal impairment (see section 5.2).
Due to the limited therapeutic experience, patients with severe renal impairment should be clinically monitored when initiating therapy with naldemedine.

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment.
Use in patients with severe hepatic impairment is not recommended (see sections 4.4 and 5.2).

Opioid pain medicinal products
There is limited experience in patients treated with opioid pain medicinal product(s) at daily doses of more than the equivalent of 400 mg of morphine. There is no experience in patients treated for constipation induced by partial opioid mu-agonists (e.g. buprenorphine).

Paediatric population
The safety and efficacy of naldemedine in children and adolescents aged below 18 years have not yet been established. No data are available.

Method of administration
Oral use.
Rizmoic should be taken once daily, with or without food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients with known or suspected gastrointestinal obstruction or perforation or patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation (see section 4.4).

4.4 Special warnings and precautions for use

Gastrointestinal perforation
Cases of gastrointestinal perforation have been reported with use of peripherally-acting opioid antagonists in patients with conditions that may be associated with localised or diffuse reduction of structural integrity of the wall of the gastrointestinal tract (e.g. peptic ulcer disease, Ogilvie's syndrome, diverticular disease and underlying malignancies of the gastrointestinal tract or peritoneal metastases). The overall risk-benefit of naldemedine should be considered in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g. Crohn's disease). Patients should be monitored for the development of severe, persistent or worsening abdominal pain. If obstruction or perforation are suspected, naldemedine must be discontinued (see section 4.3).

Gastrointestinal adverse reactions
Abdominal adverse reactions (e.g. abdominal pain, vomiting and diarrhoea) have been reported with Rizmoic. Patients should be advised to report severe, persistent or worsening symptoms to their physician. In cases of severe diarrhoea or abdominal pain, the patient should be monitored and treated for dehydration using rehydration and appropriate treatment as needed (see section 4.8).

Opioid withdrawal syndrome
Opioid withdrawal syndrome is a cluster of three or more of the following signs or symptoms: dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinorrhea, pupillary dilation or piloerection or sweating, diarrhoea, yawning, fever or insomnia. Opioid withdrawal syndrome typically develops within minutes to several days following administration of an opioid antagonist. Caution should be exercised with regards to opioid withdrawal. Patients should be advised to discontinue naldemedine and to contact their physician if opioid withdrawal occurs. Cases of possible opioid withdrawal syndrome have been reported in the naldemedine clinical programme (see section 4.8).

Patients having disruptions to the blood-brain barrier (e.g., primary brain malignancies, central nervous system (CNS) metastases or other inflammatory conditions, active multiple sclerosis and advanced Alzheimer's disease) may be at increased risk of opioid withdrawal or reduced analgesia. The overall benefit-risk of naldemedine should be considered in these patients with close monitoring for symptoms of opioid withdrawal.

Patients with cardiovascular conditions
Naldemedine was not studied in the clinical trial programme in patients who had a recent history of myocardial infarction, stroke or transient ischaemic attack within 3 months of screening. These patients should be clinically monitored when taking Rizmoic.
A QTc study performed with naldemedine in healthy volunteers did not indicate any prolongation of the QT interval. Patients with cardiovascular disease risk factors were not excluded from the naldemedine clinical trial programme, with BMI $\geq$ 30 kg/m^2, and a medical history of hypertension and/or dyslipidaemia being the most commonly reported risk factors.

Severe hepatic impairment
Naldemedine has not been studied in patients with severe hepatic impairment. The use of naldemedine is not recommended in these patients (see section 4.2).

Concomitant use with strong CYP3A inhibitors and inducers
Concomitant use of naldemedine with strong CYP3A inhibitors (e.g. grapefruit juice, itraconazole, ketoconazole, ritonavir, indinavir, saquinavir, telithromycin and clarithromycin) leads to an increase in naldemedine exposure and may increase the risk of adverse reactions. Concomitant use with strong CYP3A inhibitors should be avoided.

Concomitant use of naldemedine with strong CYP3A inducers (e.g. St. John's wort (*Hypericum perforatum*), rifampicin, carbamazepine, phenobarbital and phenytoin) leads to a decrease in naldemedine exposure and may reduce the efficacy of naldemedine. Concomitant use with strong CYP3A inducers is not recommended (see section 4.5). Concomitant use of naldemedine with moderate CYP3A inducers (e.g. efavirenz) has not been established and should be used with caution (see section 4.5).

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, and is therefore essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on naldemedine
Naldemedine is primarily metabolised by CYP3A with some contribution from UGT1A3 and is a substrate of P-glycoprotein (P-gp) (see section 5.2).

Interactions with CYP3A inhibitors
Itraconazole, a strong CYP3A inhibitor, increased exposure to naldemedine 2.9 fold that may result in an increased risk of adverse reactions.
Concomitant use of strong CYP3A inhibitors such as grapefruit juice, itraconazole, ketoconazole, ritonavir, indinavir, saquinavir, telithromycin and clarithromycin should be avoided. If use with strong CYP3A inhibitors is unavoidable, monitor for adverse reactions (see section 4.4).
Concomitant use of moderate CYP3A inhibitors such as fluconazole, may increase the plasma concentration of naldemedine. If used with moderate CYP3A inhibitors, monitor for adverse reactions.
There is no risk of interaction with concomitant use of mild CYP3A inhibitors.

Interaction with strong and moderate CYP3A inducers
Rifampicin, a strong CYP3A inducer, significantly decreased exposure to naldemedine by 83% .
Concomitant use of strong CYP3A inducers such as St. John's wort (*Hypericum perforatum*), rifampicin, carbamazepine, phenobarbital and phenytoin is not recommended. Concomitant use of naldemedine with moderate inducers (e.g. efavirenz) has not been established, and patients should be monitored (see section 4.4).

Interaction with strong P-gp inhibitors
Concomitant use of P-gp inhibitors such as cyclosporine may increase plasma concentrations of naldemedine. If naldemedine is used with strong P-gp inhibitors, monitor for adverse reactions.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of naldemedine in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
The use of naldemedine during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood brain barrier.
Naldemedine should not be used during pregnancy unless the clinical condition of the woman requires treatment with naldemedine.

Breast-feeding
It is unknown whether naldemedine/metabolites are excreted in human milk. Available data in rats have shown excretion of naldemedine in milk (see section 5.3).
At therapeutic doses, most opioids (e.g morphine, meperidine, methadone) are excreted into breast milk in minimal amounts. There is a theoretical possibility that naldemedine provokes opioid withdrawal in a breast-fed neonate whose mother is taking an opioid receptor agonist.
A risk to the suckling child cannot be excluded.
Naldemedine should not be used during breast-feeding.

Fertility
No human data on the effect of naldemedine on fertility are available. Naldemedine was found to have no clinically relevant adverse effects on fertility or reproductive performance in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Naldemedine has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions in patients with chronic non-cancer pain and OIC were abdominal pain (7.8%), diarrhoea (5.9%), nausea (3.6%), and vomiting (1.1%). The majority of these gastrointestinal adverse reactions were of mild to moderate severity and resolved without discontinuation of naldemedine treatment. One serious case of abdominal pain and one serious case of nausea were reported in patients with chronic non-cancer pain and OIC.

The most commonly reported adverse reactions in patients with cancer and OIC were diarrhoea (24.5%) and abdominal pain (3.9%). The majority of these gastrointestinal adverse reactions were of mild to moderate severity and resolved with treatment. Two serious cases of diarrhoea were reported in patients with cancer and OIC.

Tabulated list of adverse reactions
The adverse reactions with naldemedine 200 microgram tablets in patients with chronic non-cancer pain and OIC and in patients with cancer and OIC reported in clinical studies are presented in the tables according to the MedDRA system organ classification. The frequency categories are defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

iTable 1. Adverse reactions presented by System Organ Class and frequency in patients with chronic non-cancer pain and opioid-induced constipation

System Organ Class	Common	Uncommon	Rare
Immune system disorders			Hypersensitivity[a]
Gastrointestinal disorders	Diarrhoea Abdominal pain[b] Nausea Vomiting		
General disorders and administration site conditions		Opioid withdrawal syndrome	

[a]One serious report of hypersensitivity reaction was observed in clinical studies with naldemedine. The patient recovered following discontinuation from the study
[b]MedDRA Preferred Terms: abdominal pain, abdominal pain upper, abdominal pain lower and abdominal discomfort

Table 2. Adverse reactions presented by System Organ Class and frequency in patients with cancer and opioid-induced constipation

System Organ Class	Very Common	Common	Uncommon
Gastrointestinal disorders	Diarrhoea	Abdominal pain[a]	
General disorders and administration site conditions			Opioid withdrawal syndrome

[a]MedDRA Preferred Terms: abdominal pain, abdominal pain upper, abdominal pain lower and abdominal discomfort

Description of selected adverse reactions

Opioid withdrawal syndrome

Possible opioid withdrawal, defined as at least three adverse reactions potentially related to opioid withdrawal that occurred on the same day and that were not exclusively related to the gastrointestinal system, occurred in 0.8% (9/1,163) of patients with chronic non-cancer pain and OIC taking naldemedine compared to 0.2% (2/1,165) of patients taking placebo regardless of maintenance opioid treatment, and 0.6% (1/155) of patients with cancer and OIC taking naldemedine 200 micrograms compared to 0% (0/152) of patients taking placebo. Symptoms included, but were not limited to hyperhidrosis, chills, lacrimation increased, hot flush/flushing, pyrexia, sneezing, feeling cold, abdominal pain, diarrhoea, nausea, vomiting, arthralgia, myalgia, and tachycardia (see section 4.4).

Gastrointestinal disorders

Abdominal pain, diarrhoea, nausea and vomiting were the most commonly reported adverse reactions in clinical studies with patients with chronic non-cancer pain and OIC and with patients with cancer and OIC. The majority of these gastrointestinal adverse reactions were mild to moderate severity and resolved with treatment. The discontinuation rate due to gastrointestinal treatment emergent adverse events with naldemedine 200 micrograms compared to placebo was 3.2% and 1% respectively in patients with chronic non-cancer pain and OIC and 4.5% and 0% respectively for patients with cancer and OIC.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Healthy volunteers
A single dose of naldemedine up to 100 mg and multiple doses of up to 30 mg/day for 10 days were administered to healthy volunteers in clinical studies. Dose-dependent increases in gastrointestinal-related adverse reactions, including abdominal pain, diarrhoea, and nausea, were observed. These were mild or moderate in severity and resolved.

Patients with OIC
A single dose of naldemedine (0.01 mg to 3 mg) and multiple doses of 0.4 mg/day have been administered to patients with OIC in clinical studies. A patient who took a single dose of naldemedine 1 mg experienced severe drug withdrawal syndrome, including nausea and stomach cramping and was given esomeprazole and ondansetron for nausea and midazolam hydrochloride for stomach cramping. The symptoms resolved. In clinical studies, patients with OIC who were administered 0.4 mg/day (twice the recommended dose) over 4 weeks had an increased incidence of GI-related adverse drug reactions including diarrhoea and abdominal pain frequently within 1-2 days after initial dosing.

Management
There is no specific antidote for naldemedine. Naldemedine is not removed from the body by haemodialysis. In the event of an overdose, patients should be closely monitored for potential signs and symptoms of opioid withdrawal syndrome (see section 4.4) and provided with appropriate supportive care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for constipation, peripheral opioid receptor antagonists, ATC code: A06AH05.

Mechanism of action
Naldemedine is an antagonist of opioid binding at the mu-, delta-, and kappa-opioid receptors. Naldemedine functions as a peripherally-acting mu-opioid receptor antagonist in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids without reversing the central nervous system (CNS)-mediated opioid effects.
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.

Clinical efficacy and safety
The efficacy and safety of naldemedine has been established in patients with chronic non-cancer pain and OIC and in patients with cancer and OIC.

Clinical studies in patients with chronic non-cancer pain and OIC
The safety and efficacy of naldemedine was evaluated in two identical, 12-week randomised, double-blind placebo-controlled trials (Studies V9231 and V9232) in which naldemedine was used without laxatives and in a third long-term 52-week randomised, double-blind placebo-controlled trial (Study V9235) in which naldemedine was used with or without stable laxatives in patients with chronic non-cancer pain and OIC.

Patients receiving a stable opioid morphine equivalent daily dose of ≥ 30 mg for at least 4 weeks before enrollment and self-reported OIC were eligible to participate.

In Studies V9231 and V9232, OIC was confirmed through a 2-week run-in period and was defined as no more than 4 spontaneous bowel movements (SBMs) total over 14 consecutive days and <3 SBMs in a given week with at least 25% of the SBMs associated with one or more of the following conditions: (1) straining, (2) hard or lumpy stools; (3) having a sensation of incomplete evacuation; and (4) having a sensation of anorectal obstruction/blockage. In Study V9235, OIC was confirmed through a 2-week run-in period and was defined as no more than 4 SBMs total over 14 consecutive days and <3 SBMs in a given week.

A SBM was defined as a bowel movement (BM) without rescue laxative taken within the past 24 hours.

In Studies V9231 and V9232, patients had to either not be using laxatives or be willing to discontinue laxative use at the time of Screening and be willing to use only the provided rescue laxatives during the Screening and Treatment Periods. All study participants took laxatives previously for the treatment of OIC. In Study V9235, patients on a stable laxative regimen at screening (52.4%) were allowed to continue using that same regimen without change throughout the study duration. In the run-in and treatment periods for all three studies, bisacodyl was used as rescue laxative if patients had not had a BM for 72 hours and were allowed one-time use of an enema if after 24 hours of taking bisacodyl, they still had not had a BM.

Patients with evidence of significant structural abnormalities of the gastrointestinal tract were not enrolled in these studies.

A total of 547 patients in Study V9231, 551 patients in Study V9232 and 1246 patients in Study V9235 were randomised in a 1:1 ratio to receive 200 micrograms of naldemedine or placebo once daily for 12 weeks for Studies V9231 and V9232, for 52 weeks for Study V9235.

In Studies V9231, V9232 and V9235, the mean age of the subjects in these three studies was 53.2 years; 14.8% were 65 years of age or older; 62.0% were women; 80.2% were white.

In Study V9231, the three most common types of pain were back pain (62.0%); neck pain (8.3%) and osteoarthritis (5.3%). In Study V9232, they were back pain (53.6%); pain (10.2%) and arthralgia (7.8%). In Study V9235, the three most common types of pain were back pain (58.0%); osteoarthritis (9.5%) and neck pain (8.1%).

Prior to enrollment, patients had been using their current opioid for an average of 5 years. The patients who participated in Studies V9231, V9232 and V9235 were taking a wide range of opioids.
The mean baseline opioid morphine equivalent daily dosage was 132.42 mg, 120.93 mg, and 122.06 mg per day for Studies V9231, V9232 and V9235 respectively. The mean baseline SBMs was 1.31, 1.17, and 1.60, for Studies V9231, V9232 and V9235 respectively.

The primary endpoint for Studies V9231 and V9232 was the proportion of SBM responders, defined as: ≥3 SBMs per week and a change from baseline of ≥1 SBM per week for at least 9 out of the 12 study weeks and 3 out of the last 4 weeks. The primary efficacy endpoint for Study V9235 was the change in the frequency of BMs per week from baseline to Weeks 12, 24, 36 and 52.

There was a statistically significant difference for naldemedine treatment group versus placebo for the primary endpoint in Studies V9231 and V9232 (see Table 3).

There were 4 secondary endpoints in Studies V9231 and V9232 (see Table 3).

Table 3. Clinical outcomes for studies V9231 and V9232

	V9231		V9232	
	Naldemedine (N=273)	Placebo (N=272)	Naldemedine (N=276)	Placebo (N=274)
Proportion of SBM Responders	47.6%	34.6%	52.5%	33.6%
Treatment difference	13.0% (95% CI: 4.8%, 21.3%, p=0.0020*)		18.9% (95% CI: 10.8%, 27.0%, p<0.0001*)	
Change in frequency of SBMs per week (LS Mean)				
From baseline to the last 2 weeks of treatment**	3.42	2.12	3.56	2.16
From baseline to week 1**	3.48	1.36	3.86	1.69
Change in frequency of CSBMs per week (LS Mean)				
From baseline to the last 2 weeks of treatment**	2.58	1.57	2.77	1.62
Change in frequency of SBMs without straining per week (LS Mean)				
From baseline to the last 2 weeks of treatment***	1.46	0.73	1.85	1.10

CI=Confidence Interval
*Statistically significant: p-values based on the Cochran-Mantel-Haenszel test.
** p<0.0001
*** p=0.0003 for study V9231 and p=0.0011 for study V9232

For Study V9235, the efficacy of naldemedine vs. placebo was assessed as secondary endpoints by the frequency of BMs as presented in Table 4.

Table 4. Change in the frequency of BMs per week from baseline to each visit (LS Mean) ITT population in study V9235

	Naldemedine (N=621)	Placebo (N=620)
Mean frequency of BMs at baseline	2.02	2.02
Change in the Frequency of BMs per week		
Week 12*	3.70	2.42
Week 24*	3.77	2.77
Week 36*	3.88	2.88
Week 52*	3.92	2.92

*nominal p≤0.0001

The efficacy and safety were also assessed in the laxative inadequate responders (LIR) and non-LIR subgroups.

In Studies V9231 and V9232, patients who, based on concomitant medication records, were on laxative therapy prior to entering the study and who stopped its use within 30 days prior to Screening, and had self-reported OIC, were considered to be a LIR.

Additionally, patients who were not on laxatives within 30 days prior to Screening and only received rescue laxative at or after Screening were considered non-LIR. The number of patients in the LIR and non-LIR subgroups were 629 (naldemedine: 317 and placebo: 312) and 451 (naldemedine: 223 and placebo: 228) for pooled Studies V9231 and V9232. All study participants took previous laxatives at some time for the treatment of OIC prior to entering the trials V9231 or V9232.

In the LIR subgroup, a greater proportion of responders was observed with naldemedine (46.4%) compared with placebo (30.2%) and the difference between groups (16.2%) was statistically significant ($p<0.0001$).

In the non-LIR subgroup, consistent with the results in the LIR subgroup, a greater proportion of responders was observed with naldemedine (54.3%) compared with placebo (38.9%) and the difference between groups (15.6%) was statistically significant ($p=0.0009$).

For Study V9235, long term efficacy data defined as the change in frequency of BMs at week 52 from baseline, assessed as a secondary endpoint, showed that subjects in the naldemedine group had improvements in the frequency of BMs compared with subjects in the placebo group in both LIR (3.10 vs 1.90, $p=0.0210$) and non-LIR (4.26 vs 3.39, $p=0.1349$) subgroups.

Clinical studies in patients with cancer and OIC
The safety and efficacy of naldemedine was also evaluated in 2 randomised, double-blind and placebo-controlled studies (V9222 and V9236) in patients with cancer and OIC.

Subjects were required to be treated with opioids for ≥14 days prior to Screening and had to be receiving a stable dose. The studies included a 2-week Screening Period, 2-week Treatment Period and 4-week Follow-up Period. For patients receiving laxative therapy at the Screening visit, it had to be continued at a stable dose until the end of the Treatment Period. Patients were allowed to receive rescue laxative(s) as needed regardless of being on a stable laxative regimen at baseline (apart from within 24 hours of the start of the Treatment Period).

In studies V9222 and V9236, OIC was confirmed through a 2-week run-in period and was defined as ≤5 SBMs during the 14 consecutive days prior to the randomisation and ≥1 of the following bowel symptoms in ≥25% of all BMs regardless of the use of rescue laxatives: presence of straining during bowel movement, feeling of incomplete evacuation, passage of hard stools or small pellets.

In studies V9222 and V9236, the mean age of the subjects was 64.3 years; 51.8% were 65 years of age or older; 39.4% were women and 97.1% were Japanese.

Naldemedine 200 micrograms or placebo was administered for 2 weeks to cancer patients with OIC. The primary endpoint for Study V9236 and the secondary endpoint, without multiplicity adjustment, for Study V9222 were the proportion of SBM responders during the 2-week Treatment Period. A responder was defined as a patient with ≥3 frequency of SBMs per week and an increase from baseline ≥1 SBM per week during the 2-week Treatment Period

Table 5. Proportion of SBM responders in patients with cancer and OIC during the 2-week treatment period (Studies V9222 and V9236)

	V9222			V9236		
	Naldemedine (N=58)	Placebo (N=56)	Treatment Difference [95% Cl]	Naldemedine (N=97)	Placebo (N=96)	Treatment Difference [95% Cl]
Patients responding, n (%)	45 (77.6%)	21 (37.5%)	40.1% [23.5%, 56.7%]	69 (71.1%)	33 (34.4%)	36.8% [23.7%, 49.9%]
p value*			<0.0001			<0.0001

*Statistically significant: p-values based on the Chi-square test.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Rizmoic in one or more subsets of the paediatric population in the treatment of opioid-induced constipation (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Naldemedine is absorbed with a time to achieve peak plasma concentration of approximately 0.75 hours in the fasted state. The absolute bioavailability of naldemedine has not been established. The absolute bioavailability of naldemedine is estimated to be in the range of 20% to 56%.

There is no clinically significant food effect. The peak plasma concentration was reduced by 35% and time to achieve peak plasma concentration was delayed from 0.75 hours in the fasted state to 2.5 hours in the fed state, whereas no significant difference was observed in the area under the plasma concentration-time curve by food intake. Based on these data, naldemedine can be taken with or without food (see section 4.2).

Distribution
Naldemedine is highly bound to serum proteins, predominantly to human serum albumin and to a lesser extent to α1-acid-glycoprotein and γ-globulin, with a mean protein binding ratio in humans of 93.2%. The apparent volume of distribution is approximately 155 litres.

Biotransformation
Naldemedine is primarily metabolized by CYP3A to nor-naldemedine, with a minor contribution from UGT1A3 to form naldemedine 3-G.

Following oral administration of [14C]-labelled naldemedine, the primary metabolite in plasma was nor-naldemedine, with a relative exposure compared to naldemedine of approximately 9 to 13%. Naldemedine 3-G was a minor metabolite in plasma, with a relative exposure to naldemedine of less than 3%.

Naldemedine also undergoes cleavage in the gastrointestinal tract to form benzamidine and naldemedine carboxylic acid.

In *in vitro* studies at clinically relevant concentrations, naldemedine did not inhibit the major CYP enzymes (including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A, or CYP4A11 isozymes) and is not an inhibitor of OCT1, OCT2, BCRP, P-gp, MATE1, MATE2-K or BSEP transporters. Naldemedine did not cause significant induction of CYP1A2, CYP2B6 or CYP3A4 isozymes. Therefore, treatment with naldemedine is not expected to alter the pharmacokinetics of co-administered medicines that are substrates of these enzymes and transporters. *In vitro* data also showed that naldemedine is not a direct inhibitor of OATP1B1, OATP1B3, OAT1 and OAT3 transporters.

Elimination
The apparent terminal elimination half-life of naldemedine is approximately 11 hours, and the apparent total clearance (CL/F) of naldemedine is 8.4 L/h. Following oral administration of radio-labelled naldemedine, 57.3% and 34.8% of the dose was excreted in urine and faeces for the [oxadiazole-^{14}C]-naldemedine and 20.4% and 64.3% of the dose was excreted as the [carbonyl-^{14}C]-naldemedine in urine and faeces, respectively. Approximately 20% of the naldemedine dose is excreted unchanged in urine.

Linearity/non-linearity
The peak plasma concentration and area under the plasma concentration-time curve increased in an almost dose-proportional manner within the dose range of 0.1 to 100 mg. A slight accumulation (1 to 1.3-fold) for peak plasma concentration and area under the plasma concentration–time curve was observed after once daily multiple dose administration in the fasted state for 10 days.

Pharmacokinetics in subpopulations
Age, gender, body weight and race
A population pharmacokinetic analysis from clinical studies with naldemedine did not identify a clinically meaningful effect of age, gender, body weight or race on the pharmacokinetics of naldemedine.

The pharmacokinetics of naldemedine in the paediatric population has not been studied (see section 4.2).

Renal impairment
The pharmacokinetics of naldemedine after administration of a single 200 microgram dose of naldemedine was studied in subjects with mild, moderate or severe renal impairment, or with end-stage renal disease (ESRD) requiring haemodialysis, and compared with healthy subjects with normal renal function.

The pharmacokinetics of naldemedine between subjects with mild, moderate or severe renal impairment, or subjects with ESRD requiring hemodialysis and healthy subjects with normal renal function were similar.

Plasma concentrations of naldemedine in subjects with ESRD requiring dialysis were similar when naldemedine was administered either pre- or post-haemodialysis, indicating that naldemedine was not removed from the blood by haemodialysis.

Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of a single 200 microgram dose of naldemedine was studied in subjects with hepatic impairment classified as mild (Child-Pugh class A) or moderate (Child-Pugh class B) and compared with healthy subjects with normal hepatic function. The pharmacokinetics of naldemedine between subjects with mild or moderate hepatic impairment and healthy subjects with normal hepatic function were similar. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of naldemedine was not evaluated.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and embryo-fetal development.

In the rat fertility and early embryonic development study, prolongation of the dioestrous phase was observed at 10 mg/kg/day and above, but was not observed at 1 mg/kg/day (12 times the exposure [$AUC_{0\text{-}24hr}$] in humans at an oral dose of 200 micrograms). The effect on oestrous cycle is not

considered clinically relevant at the proposed therapeutic dose. No adverse effects were observed in male or female fertility and reproductive performance at up to 1000 mg/kg/day (in excess of 16,000 times the exposure [$AUC_{0\text{-}24hr}$] in humans at an oral dose of 200 micrograms).

In the pre- and postnatal development study in rats, one dam died at parturition at 1000 mg/kg/day, and poor nursing, suppression of body weight gain and decrease in food consumption were noted at 30 and 1000 mg/kg/day. Decreases in the viability index on Day 4 after birth were noted at 30 and 1000 mg/kg/day and low body weights and delayed pinna unfolding were noted at 1000 mg/kg/day in pups. There was no adverse effect on pre- and postnatal development at 1 mg/kg/day (12 times the exposure [$AUC_{0\text{-}24hr}$] in humans at an oral dose of 200 micrograms).

Placental transfer of [carbonyl-^{14}C]-naldemedine-derived radioactivity was observed in pregnant rats. [Carbonyl-^{14}C]-naldemedine-derived radioactivity was excreted into milk in lactating rats.

In juvenile toxicity studies in rats, at the same dose levels, exposure in juvenile animals (PND 10) was increased compared to adult animals (2.3 to 7.4-fold). Novel histopathology findings were observed at all doses tested in female rats in ovaries (tertiary follicles/luteal cysts) in addition to irregular oestrous cycles, hyperplasia of mammary gland, and vaginal mucification already observed in adult animals (the lowest dose tested corresponded to an exposure margin of 6 or more, depending on the age of the pups). Three-day earlier vaginal opening indicative of an early onset of sexual maturity was also observed, but only at high exposures considered sufficiently in excess of the maximum human exposure at an oral dose of 200 micrograms.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Mannitol
Croscarmellose sodium
Magnesium stearate

Film coating
Hypromellose
Talc
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Aluminium/aluminium blister containing 7 or 14 film-coated tablets.

Pack sizes of 7, 28 or 84 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Shionogi B.V.
Kingsfordweg 151
1043GR Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1291/001
EU/1/18/1291/002
EU/1/18/1291/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release
Manufacturing Packaging Farmaca (MPF) bv
Appelhof 13
NL-8465 RX Oudehaske
8465 RX Oudehaske
Netherlands

Manufacturing Packaging Farmaca (MPF) bv
Neptunus 12
NL-8448 CN Heerenveen
8448 CN Heerenveen
Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.
The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Date of preparation: February 2019

ANNEX III

LABELLING AND PACKAGE LEAFLET

Date of preparation: February 2019

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rizmoic 200 micrograms film-coated tablets

naldemedine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 micrograms naldemedine (as tosylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
28 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Shionogi B.V.
Kingsfordweg 151
1043GR Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1291/001	7 film-coated tablets
EU/1/18/1291/002	28 film-coated tablets
EU/1/18/1291/003	84 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rizmoic

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Rizmoic 200 micrograms tablets

naldemedine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Shionogi

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Date of preparation: February 2019

Package leaflet: Information for the patient

Rizmoic 200 micrograms film-coated tablets
naldemedine

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rizmoic is and what it is used for

Rizmoic contains the active substance naldemedine.

It is a medicine used in adults to treat constipation caused by pain medicines, called opioids (e.g morphine, oxycodone, fentanyl, tramadol, codeine, hydromorphone, methadone).

Your opioid pain medicine may cause the following symptoms:
- reduction in how often you pass stools
- hard stools
- stomach ache
- pain in the rectum when pushing hard stools out
- a feeling that the bowel is still not empty after passing stools.

Rizmoic can be used in patients using an opioid medicine for cancer pain or long term non-cancer pain after they have previously been treated with a laxative.

2. What you need to know before you take Rizmoic

Do not take Rizmoic:
- if you are allergic to naldemedine or any of the other ingredients of this medicine (listed in section 6).
- if your bowel is blocked or perforated, or if there is a high risk of your bowel becoming blocked, as a blockage may cause a hole to develop in the bowel wall.

Do not take this medicine if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Rizmoic.

Warnings and precautions

Talk to your doctor or pharmacist **before taking** Rizmoic:
- if you suffer from a disease which may affect your bowel wall such as:
  - a stomach ulcer;
  - an enlarged colon due to a condition known as Ogilvie's syndrome;
  - diverticulitis (an illness where your gut is inflamed);
  - cancer of the bowel or peritoneum. The peritoneum is the lining of your gut area.
  - a disease causing severe inflammation of the digestive tract such as Crohn's disease .

- if you have cancer of the brain or central nervous system, multiple sclerosis, or Alzheimer's disease. If you have these conditions and develop opioid withdrawal symptoms (see section 4) or if the opioid medicine no longer controls your pain, contact your doctor immediately.

- if you have had a heart attack within the last 3 months or if you have other severe problems with your heart which cause daily symptoms

- if you have severe liver disease such as alcoholic liver disease, viral liver infection or impaired liver function.

- if you are taking certain medicines such as itraconazole to treat fungal infections, or an antibiotic called rifampicin to treat tuberculosis and other infections. See 'Other medicines and Rizmoic'.

If any of the above apply to you, or you are not sure, talk to your doctor or pharmacist before taking Rizmoic.

Talk to your doctor or pharmacist immediately **whilst taking** Rizmoic:
- if you develop **severe, lasting or worsening stomach pain** as this could be a symptom of developing a hole in your bowel wall. Speak to your doctor immediately and stop taking Rizmoic.
- if you suffer from **symptoms of opioid withdrawal syndrome** (see section 4 Possible side effects) which can develop within minutes to several days after taking a medicine such as Rizmoic. Stop taking Rizmoic and contact your doctor if you develop opioid withdrawal symptoms.
- if you have **severe diarrhoea or stomach ache**, tell your doctor, so that the doctor can monitor you and treat you with rehydration and appropriate medicines if needed.

Children and adolescents
This medicine is not for children or adolescents under the age of 18 years because the effects of the medicine in children and adolescents are not known.

Other medicines and Rizmoic
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Talk to your doctor or pharmacist if you are taking any of the following medicines:
- Rifampicin, clarithromycin or telithromycin (antibiotic medicines)
- Itraconazole or ketoconazole (medicines to treat fungal infections)
- Ritonavir, indinavir or saquinavir (medicines for HIV infection)
- Phenytoin, carbamazepine, phenobarbital (medicines to treat epilepsy)
- St John’s wort (*Hypericum perforatum*), a herbal medicine used for depression

Using these medicines with Rizmoic may affect the way naldemedine works or increase its side effects.

Rizmoic with drink
You should not drink large amounts of grapefruit juice whilst taking Rizmoic.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. The effects of the medicine in pregnant women are not known. Your doctor will advise you about whether you can use Rizmoic if you are pregnant.

Do not breast-feed during treatment with Rizmoic as it is not known if naldemedine passes into breast milk. Talk to your doctor if you are already breast-feeding.

Driving and using machines
Rizmoic has no influence on your ability to drive or to use machines.

Rizmoic contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Rizmoic

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

- The recommended dose is one 200 microgram tablet once daily.
- You can take Rizmoic with or without laxatives.
- You can take Rizmoic at any time of the day, with food or between meals. However, once you start taking the medicine, take it at around the same time each day.
- There is no need to alter the dose of your opioid medicine before starting Rizmoic.

If you stop taking your opioid medicine
You should stop taking Rizmoic when you stop taking your opioid pain medicine.

If you take more Rizmoic than you should
If you have taken more Rizmoic than you should, talk to your doctor or go to the hospital. You will be monitored for opioid withdrawal symptoms (see section 2, under 'Warnings and Precautions', and section 4).

If you forget to take Rizmoic
If you miss a tablet of Rizmoic, take it as soon as you remember.
However if it is less than 12 hours until your next dose, skip the missed dose, and wait until it is time to take your next tablet.
Do not take a double dose to make up for a forgotten tablet.

If you stop taking Rizmoic
Stopping Rizmoic while continuing to take your opioid medicine may cause the constipation to return. Talk to your doctor if you stop taking Rizmoic.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Rizmoic and contact your doctor if you get a combination of 3 or more of the following symptoms of **opioid withdrawal** on the same day:

- feeling depressed
- nausea (feeling sick) or vomiting
- achy muscles
- watery eyes or runny nose
- pupils dilating
- hairs of the skin standing on end
- sweating
- diarrhoea
- yawning
- fever
- inability to sleep

The following side effects may happen with this medicine:

If you are being treated with an opioid medicine for chronic non-cancer pain.

Rare (may affect up to 1 in 1,000 people):

- If you experience a serious allergic reaction, stop taking Rizmoic and see a doctor or go to a hospital straight away.. Serious allergic reactions include: swelling of the hands, feet, ankles, face, lips or throat which may cause difficulty swallowing or breathing, itching of the skin and nettle rash.

Common (may affect up to 1 in 10 people):

- diarrhoea
- stomach pain
- nausea (feeling sick)
- vomiting

If you are being treated with an opioid medicine for cancer.

Very common (may affect more than 1 in 10 people):

- diarrhoea

Common:

- stomach pain

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rizmoic

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blisters after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect the tablets from light and moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rizmoic contains
- Each tablet contains 200 micrograms of naldemedine (as tosylate).
- The other ingredients are:
  Tablet core: Mannitol, croscarmellose sodium (see section 2 under 'Rizmoic contains sodium') and magnesium stearate.
  Film coating: hypromellose , talc and yellow iron oxide (E172).

What Rizmoic looks like and contents of the pack
Rizmoic is a round, approximately 6.5 mm diameter, yellow film-coated tablet debossed with '222' and the Shionogi logo on one side and '0.2' on the other side.

The medicine is available in aluminium blisters, containing 7 or 14 tablets.
Pack sizes of 7, 28 or 84 tablets.
Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder
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Kingsfordweg 151
1043GR Amsterdam
The Netherlands

Manufacturer
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Heerenveen,
8448CN,
The Netherlands

Manufacturing Packaging Farmaca (MPF) B.V.,
Appelhof 13,
Oudehaske,
8465RX,
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.