ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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
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 (see section 4.4).

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).

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 in the post-marketing setting (see section 4.8), including fatal cases, when naldemedine was used in patients who were at an increased risk of gastrointestinal (GI) perforation, (e.g. diverticular disease and underlying malignancies of the gastrointestinal tract or peritoneal metastases).
Naldemedine must not be used in patients with known or suspected GI obstruction or in patients at increased risk of recurrent obstruction, due to the potential for GI perforation (see section 4.3).
Caution with regards to the use of naldemedine should be exercised in patients with any conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g. peptic ulcer disease, Ogilvie's syndrome, malignancy of the GI tract, Crohn's disease). The overall benefit risk for each patient should be taken into account. 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 renal impairment

Due to limited therapeutic experience in patients with severe renal impairment, these patients should be clinically monitored when initiating therapy with naldemedine (see section 4.2).

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).

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).
Caution should be exercised when treating these patients.

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, that is to say 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.

Table 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	Unknown
Immune system disorders			Hypersensitivity[a]	
Gastrointestinal disorders	Diarrhoea Abdominal pain[b] Nausea Vomiting			Gastrointestinal perforation
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	Unknown
Gastrointestinal disorders	Diarrhoea	Abdominal pain[a]		Gastrointestinal perforation
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:

Pharmacovigilance Department
The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products

Al. Jerozolimskie 181C
PL-02 222 Warszawa
Tel.: + 48 22 49 21 301
Faks: + 48 22 49 21 309
Website: https://smz.ezdrowie.gov.pl.

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 opioid 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 dose 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

	V9231		V9232	
	Naldemedine (N=273)	Placebo (N=272)	Naldemedine (N=276)	Placebo (N=274)
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 metabolised 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 OATP1B1, OATP1B3, OAT1, OAT3, 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.

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, 10 or 14 film-coated tablets.
Pack sizes of 7, 10, 28, 30, 84 or 100 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.
Herengracht 464, 1017CA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1291/001
EU/1/18/1291/002
EU/1/18/1291/003
EU/1/18/1291/004
EU/1/18/1291/005
EU/1/18/1291/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 February 2019
Date of latest renewal: 03 November 2023

10. DATE OF REVISION OF THE TEXT

03 November 2023

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