

Summary of Investigation Results

Preparations containing proton pump inhibitor

Non-proprietary name	Non-proprietary name	Brand name (marketing authorization holder)
Brand name	See Attachment.	See Attachment.
Japanese market launch	See Attachment.	
Indications	See Attachment.	
Summary of revisions	1. A cautionary statement regarding “Hypomagnesaemia” should be added to the 8. IMPORTANT PRECAUTIONS section. 2. “Hypomagnesaemia” should be added to the 11.1 Clinically Significant Adverse Reactions section in the 11. ADVERSE REACTIONS.	
Investigation results and background of the revision	Cases involving hypomagnesaemia were evaluated. Cases in which a causal relationship between preparations containing proton pump inhibitor and hypomagnesaemia was reasonably possible have been reported. As a result of consultation with expert advisors regarding the causality assessment of the cases and the necessity of revision of PRECAUTIONS, the MHLW/PMDA concluded that revision of PRECAUTIONS was necessary.	
Reference: Number of cases* involving hypomagnesaemia reported in Japan* ²	a. A total of 1 case has been reported to date (including 0 cases in which a causal relationship between the drug and the event was reasonably possible). No deaths have been reported to date. b. A total of 0 cases have been reported to date. c. A total of 3 cases have been reported to date (including 2 cases in which a causal relationship between the drug and the event was reasonably possible). No deaths have been reported to date. d. A total of 6 cases have been reported to date (including 5 cases in which a causal relationship between the drug and the event was reasonably possible). No deaths have been reported to date. e. A total of 12 cases have been reported to date (including 5 cases in which a causal relationship between the drug and the event was reasonably possible). No deaths have been reported to date. f. A total of 17 cases have been reported to date (including 8 cases in which a causal relationship between the drug and the event was reasonably possible). No deaths have been reported to date.	

*: Cases collected in PMDA's safety database for drugs.

Among cases reported to the regulatory authority with MedDRA PTs "Hypomagnesaemia, Blood magnesium decreased, and Magnesium deficiency," those of Grade 3 or higher according to CTCAE (ver. 6.0) and in which blood magnesium levels were measured at multiple time points after discontinuation of the proton pump inhibitor were retrieved.

*2: Since multiple cases for which a proton pump inhibitor alone was used and the causal relationship with the proton pump inhibitor could not be ruled out have been identified, the accumulation status of the pre-packaged product and combination products of g through j was not confirmed.

The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the "Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

Attachment

No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
a.	Omeprazole	Omepral Tablets 10, 20, and others	TAIYO Pharma Co., Ltd., and others	Tablets 10 February 2001 Tablets 20 April 1991	< Omepral Tablets 10, Omeprazon Tablets 10 mg > ○ Gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux esophagitis, non-erosive reflux disease, Zollinger-Ellison syndrome ○ Aid to eradication of <i>Helicobacter pylori</i> in the following conditions Gastric ulcer, duodenal ulcer, gastric MALT lymphoma, immune thrombocytopenia, stomach after endoscopic treatment of early gastric cancer, and <i>Helicobacter pylori</i> gastritis < Omepral Tablets 20, Omeprazon Tablets 20 mg > ○ Gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux esophagitis, Zollinger-Ellison syndrome ○ Aid to eradication of <i>Helicobacter pylori</i> in the following conditions Gastric ulcer, duodenal ulcer, gastric MALT lymphoma, immune thrombocytopenia, stomach after endoscopic treatment of early gastric cancer, and <i>Helicobacter pylori</i> gastritis
		Omeprazon Tablets 10 mg, 20 mg, and others	Tanabe Pharma Corporation, and others	Tablets 10 mg February 2001 Tablets 20 mg April 1991	
b.	Omeprazole sodium	Omeprazole for Injection 20 mg "Nichi-iko"	Nichi-Iko Pharmaceutical Co., Ltd.	November 2010	○ The following diseases for which oral administration of other medicine is unsuitable: Gastric ulcer, duodenal ulcer, acute stress ulcer and acute gastric mucosal lesion with bleeding ○ Zollinger-Ellison syndrome for which oral administration of other medicine is unsuitable
		Omeprazole for Injection 20 mg "NP"	NIPRO CORPORATION		
		Omeprazole for Injection "TYK"	T's Seiyaku Co., Ltd.,		
c.	Rabeprazole sodium	Pariet tablets 5 mg, 10 mg, 20	Eisai Co., Ltd., and others	tablets 5 mg February 2015	< tablets 5 mg, tablets 10 mg > ○ Gastric ulcer, duodenal ulcer,

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		mg, and others		tablets 10 mg December 1997 tablets 20 mg December 1997	anastomotic ulcer, reflux esophagitis, Zollinger-Ellison syndrome, non-erosive reflux disease, and prevention of recurrence of gastric ulcer or duodenal ulcer in patients treated with low-dose aspirin ○ Aid to eradication of <i>Helicobacter pylori</i> in the following conditions Gastric ulcer, duodenal ulcer, gastric MALT lymphoma, immune thrombocytopenia, stomach after endoscopic treatment of early gastric cancer, and <i>Helicobacter pylori</i> gastritis < tablets 20 mg > Gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux esophagitis, and Zollinger-Ellison syndrome
d.	Lansoprazole	Takepron OD Tablets 15, 30, Takepron capsules 15, 30, Takepron Intravenous 30 mg, and others	T's Seiyaku Co., Ltd., and others	OD Tablets 15, OD Tablets 30 June 2002 capsules 15, capsules 30 December 1992 Intravenous 30 mg December 2006	< Takepron OD Tablets 15, Takepron capsules 15 > ○ Gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux esophagitis, Zollinger-Ellison syndrome, non-erosive reflux disease, prevention of recurrence of gastric ulcer or duodenal ulcer in patients treated with low-dose aspirin, and prevention of recurrence of gastric ulcer or duodenal ulcer in patients treated with nonsteroidal anti-inflammatory drugs ○ Aid to eradication of <i>Helicobacter pylori</i> in the following conditions Gastric ulcer, duodenal ulcer, gastric MALT lymphoma, immune thrombocytopenia, stomach after endoscopic treatment of early gastric cancer, and <i>Helicobacter pylori</i> gastritis < Takepron OD Tablets 30, Takepron capsules 30 > ○ Gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux esophagitis,

					Zollinger-Ellison syndrome ○ Aid to eradication of <i>Helicobacter pylori</i> in the following conditions Gastric ulcer, duodenal ulcer, gastric MALT lymphoma, immune thrombocytopenia, stomach after endoscopic treatment of early gastric cancer, and <i>Helicobacter pylori</i> gastritis < Intravenous 30 mg > The following diseases for which oral administration of other medicine is unsuitable: Gastric ulcer, duodenal ulcer, acute stress ulcer and acute gastric mucosal lesion with bleeding
e.	Esomeprazole magnesium hydrate	Nexium Capsules 10 mg, 20 mg, Nexium Granules for Suspension 10 mg, 20 mg, and others	AstraZeneca K.K., and others	Capsules 10 mg, Capsules 20 mg September 2011 Granules for Suspension 10 mg, Granules for Suspension 20 mg April 2018	< Nexium Capsules 10 mg, Nexium Granules for Suspension 10 mg > ○ Gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux esophagitis, non-erosive reflux disease, Zollinger-Ellison syndrome, prevention of recurrence of gastric ulcer or duodenal ulcer in patients treated with nonsteroidal anti-inflammatory drugs, and prevention of recurrence of gastric ulcer or duodenal ulcer in patients treated with low-dose aspirin ○ Aid to eradication of <i>Helicobacter pylori</i> in the following conditions Gastric ulcer, duodenal ulcer, gastric MALT lymphoma, immune thrombocytopenia, stomach after endoscopic treatment of early gastric cancer, and <i>Helicobacter pylori</i> gastritis < Nexium Capsules 20 mg, Nexium Granules for Suspension 20 mg > ○ Gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux esophagitis, Zollinger-Ellison syndrome, prevention of

					recurrence of gastric ulcer or duodenal ulcer in patients treated with nonsteroidal anti-inflammatory drugs, and prevention of recurrence of gastric ulcer or duodenal ulcer in patients treated with low-dose aspirin ○ Aid to eradication of <i>Helicobacter pylori</i> in the following conditions Gastric ulcer, duodenal ulcer, gastric MALT lymphoma, immune thrombocytopenia, stomach after endoscopic treatment of early gastric cancer, and <i>Helicobacter pylori</i> gastritis
f.	Vonoprazan fumarate	Takecab OD Tablets 10 mg, 20 mg, Takecab Tablets 10mg, 20 mg	Takeda Pharmaceutical Company Limited	OD Tablets 10 mg, OD Tablets 20 mg July 2023 Tablets 10 mg, Tablets 20 mg February 2015	○ Gastric ulcer, duodenal ulcer, reflux esophagitis, prevention of recurrence of gastric or duodenal ulcer in patients treated with low-dose aspirin, prevention of recurrence of gastric or duodenal ulcer in patients treated with nonsteroidal anti-inflammatory drugs ○ Aid to eradication of <i>Helicobacter pylori</i> in the following conditions Gastric ulcer, duodenal ulcer, gastric MALT lymphoma, immune thrombocytopenia, stomach after endoscopic treatment of early gastric cancer, and <i>Helicobacter pylori</i> gastritis
g.	Aspirin/lansoprazole combination drug	Takelda Combination Tablets	T's Seiyaku Co., Ltd.	June 2014	Inhibition of thrombus and embolus formation (limited to patients with previous history of gastric or duodenal ulcer) in patients with the following diseases or those who have undergone operation: • Patients with angina (chronic stable angina, unstable angina), myocardial infarction, ischemic cerebrovascular disorder (transient ischemic attack [TIA], cerebral infarction) • Patients who have undergone coronary artery bypass grafting (CABG) or percutaneous transluminal

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					coronary angioplasty (PTCA)
h.	Aspirin/vonoprazan fumarate combination drug	Cabpirin Combination Tablets	Takeda Pharmaceutical Company Limited	May 2020	Inhibition of thrombus/embolization formation in the following diseases or post-operations (for use only in patients with a history of gastric ulcer or duodenal ulcer): • Angina pectoris (chronic stable angina, unstable angina), myocardial infarction, or ischemic cerebrovascular disease (transient ischemic attack [TIA], cerebral infarction) • Patients who have undergone coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA)
i.	Vonoprazan fumarate/amoxicillin hydrate/clarithromycin	Vonosap Pack 400, 800	Takeda Pharmaceutical Company Limited	June 2016	< Applicable microorganisms > Strains of <i>Helicobacter pylori</i> susceptible to amoxicillin and clarithromycin < Applicable conditions > <i>Helicobacter pylori</i> infection in patients with gastric ulcer, duodenal ulcer, gastric MALT lymphoma, immune thrombocytopenia, or in the stomach after endoscopic treatment of early-stage gastric cancer, and <i>Helicobacter pylori</i> gastritis
j.	Vonoprazan fumarate/amoxicillin hydrate/metronidazole	Vonopion Pack	Takeda Pharmaceutical Company Limited	June 2016	< Applicable microorganisms > Strains of <i>Helicobacter pylori</i> susceptible to amoxicillin and metronidazole < Applicable conditions > <i>Helicobacter pylori</i> infection in patients with gastric ulcer, duodenal ulcer, gastric MALT lymphoma, immune thrombocytopenia, or in the stomach after endoscopic treatment of early-stage gastric cancer, and <i>Helicobacter pylori</i> gastritis