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Eisai Co., Ltd.

EISAI RECEIVES APPROVAL FOR INDICATION EXPANSION OF PROTON PUMP INHIBITOR PARIET® FOR USE IN PREVENTION OF RECURRENT GASTRIC OR DUODENAL ULCER CAUSED BY LOW-DOSE ASPIRIN THERAPY AND ADDITIONAL 5 MG TABLET FORMULATION IN JAPAN

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that it has received approval of a new indication for proton pump inhibitor Pariet® Tablets 10 mg (rabeprazole sodium, "Pariet") in Japan for use in the prevention of recurrent gastric or duodenal ulcers caused by low-dose aspirin therapy. In addition, Eisai has also received approval of a 5 mg tablet formulation with the same indication as Pariet Tablets 10 mg.

In recent years, the aging of Japan's population has led to an increase in the number of patients requiring long-term low-dose aspirin therapy to prevent recurrent thrombotic events in the heart or brain. At the same time, however, low-dose aspirin administration is also associated with the development of mucosal injuries in the upper gastrointestinal tract. As it is often difficult to discontinue low-dose aspirin administration in patients, it is therefore important from a clinical standpoint to work to prevent mucosal injuries from developing in the upper gastrointestinal tract while continuing to administer treatment to prevent cardiovascular and cerebrovascular events.

The data used in the application was from a Phase II/III study (Study 308 / Study 309) on patients who required long-term administration of low-dose aspirin and who were confirmed to also have a history of gastric or duodenal ulcers. The results of Study 308 showed that cumulative recurrence rates of gastric or duodenal ulcers over 24 weeks (the study's primary endpoint) in the 5 mg and 10 mg Pariet groups were 2.8% and 1.4%, respectively, compared to 21.7% for the comparator group (teprenone). Thus, both Pariet groups demonstrated a significantly better preventative effect than the comparator group ($p<0.001$ for both Pariet groups vs. the comparator group)[1]. Furthermore, in Study 309 which examined the long term administration of Pariet 5 mg and 10 mg for a maximum of 52 weeks after initial treatment of 24 weeks, both dosage groups maintained a preventative effect over the whole 76 week maximum treatment period. The most commonly reported side effects (5 or more cases observed) in both Study 308 and 309 were diarrhea and constipation, and this was consistent with the known safety profile of Pariet. In addition, the registration validity period for this indication for Pariet is 4 years.

Currently approved in more than 100 countries and territories worldwide, Pariet was first launched in Japan in 1997, where it is indicated for multiple uses, including for the treatment of gastric ulcer, duodenal ulcer, reflux esophagitis, non-erosive gastroesophageal reflux disease, and as an adjunct therapy in various types of *Helicobacter pylori* (*H. pylori*) eradication, including in patients with gastric ulcer, duodenal ulcer, or *H. pylori* gastritis.

By gaining this approval, Eisai aims to increase the clinical value of the drug so as to further contribute to the range of treatment options available to patients with acid-related diseases.

[1] R. Iwakiri, et al. *Alimentary Pharmacology and Therapeutics* 2014; 40: 780-95

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[Notes to editors]

1. About Pariet®

Pariet is a proton pump inhibitor (PPI) that was discovered and developed by Eisai. First launched in Japan in 1997, it is approved in more than 100 countries and territories worldwide. In Japan, Pariet is available in 10 mg and 20 mg tablet formulations and is indicated for multiple uses, including for the treatment of gastric ulcer, duodenal ulcer, reflux esophagitis, non-erosive gastroesophageal reflux disease, and as an adjunctive therapy in various types of *Helicobacter pylori* (*H. pylori*) eradication, including in patients with gastric ulcer, duodenal ulcer, or *H. pylori* gastritis. In addition, in December 2010, Eisai was granted domestic approval for additional dosage and administration for Pariet as twice-daily 10 mg and twice-daily 20 mg treatment regimens for patients with reflux esophagitis who are unable to obtain satisfactory relief with conventional PPI treatment. Most recently, Eisai received marketing authorization in Japan in August 2013 for two types of triple formulation packs (combination packs) for *H. pylori* eradication, both of which contain Pariet Tablets 10 mg, and in February 2014 launched the products Rabecure® Pack 400 and Rabecure Pack 800 for use in primary *H. pylori* eradication, as well as Rabefine® Pack for use in secondary *H. pylori* eradication. Among the most commonly reported adverse reactions are rash, constipation, diarrhea, and headache.

Eisai is also conducting a Phase III study in Japan on Pariet as a maintenance therapy for patients with reflux esophagitis resistant to PPI treatment.

2. Details of Marketing Approval (New Information Related to Additional Indication Underlined)

1) Product Name

<u>Pariet Tablets 5 mg</u>, Pariet Tablets 10 mg

2) Indications

Treatment of gastric ulcer, duodenal ulcer, anastomotic ulcer, reflux esophagitis, Zollinger-Ellison syndrome, non-erosive gastroesophageal reflux disease, <u>prevention of recurrent gastric or duodenal ulcers caused by low-dose aspirin therapy</u>

As an adjunct to *H. pylori* eradication in the following diseases:

Gastric ulcer, duodenal ulcer, gastric MALT lymphoma, idiopathic thrombocytopenic purpura, the stomach after endoscopic resection of early-stage gastric cancer, and *H. pylori* gastritis

3) Dosage and Administration (this excerpt is taken only from the section on the prevention of recurrent gastric or duodenal ulcers caused by low-dose aspirin therapy)

<u>For the prevention of recurrent gastric or duodenal ulcers caused by low-dose aspirin therapy</u>

<u>The usual adult dose for oral use is 5 mg of rabeprazole sodium administered once daily. However, the dosage may be increased up to 10 mg orally once daily depending on the severity of symptoms.</u>

3. About the Phase II/III ClinicalStudy (Study 308 / Study 309)

1) Study 308

Study design:	A multicenter, randomized, parallel-group, double-blind comparative trial of Pariet vs. teprenone
Study population:	Patients with a history of gastric or duodenal ulcer receiving long administration of low-dose aspirin, 472 subjects
Primary objective:	To evaluate the effect of preventing recurrence of gastric or duodenal ulcers by administering Pariet and examine the superiority of Pariet over Teprenone.
Treatment administered:	Treatment with either Pariet 5 mg once daily, Pariet 10 mg once daily, or teprenone 50 mg three times daily
Duration of treatment:	24 weeks
Primary endpoint:	Cumulative recurrence rate of gastric or duodenal ulcers

2) Study 309

Study design:	A multicenter, randomized, parallel-group, open-label trial of long term treatment with Pariet
Study population:	Patients confirmed to have no recurrence of gastric or duodenal ulcer at the end of 24 weeks of treatment in Study 308 and agree to transfer to Study 309, 328 subjects
Primary objective:	Evaluate the safety and efficacy of Pariet administered adjunctively long-term with low-dose aspirin
Treatment administered:	Treatment with Pariet 5 mg or 10 mg once daily (patients who were in the Pariet treatment arm in Study 308 continued with the same dosage, patients who were in the comparator treatment arm were given either Pariet 5 mg or Pariet 10 mg
Duration of treatment:	28-52 weeks (maximum 76 weeks including Study 308)
Primary endpoint:	Long-term safety