1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Prazaxa® Capsules			
Name of active ingredient: Dabigatran etexilate			
Report date: 04 July 2017	**Study number:** 1160.130	**Version/Revision:** Version 1.0	**Version/Revision date:** Not applicable
Title of study:	Post-Marketing Surveillance on the Long-Term Use of Prazaxa® Capsules in patients with nonvalvular atrial fibrillation		
Keywords:			
Rationale and background:	In Japan, post-approval execution of post-marketing surveillance (PMS) is requested by the Japanese Pharmaceutical Affairs Law (J-PAL) in order to accumulate safety and efficacy data for re-examination. This was a regulatory required PMS to evaluate safety (including bleeding risks) in patients with a combination therapy of Prazaxa® and any antiplatelet drugs, in elderly patients, and in patients with renal dysfunction.		
Research question and objectives:	The study objective was to investigate the safety and efficacy of long-term use of Prazaxa® Capsules in patients with nonvalvular atrial fibrillation for preventing the occurrence of ischemic stroke or systemic embolism (SEE).		
Study design:	Non-interventional, prospective, observational The analyses in this PMS were descriptive and exploratory by nature. No formal statistical inference was made.		
Setting:	Planned number of site: 700 Planned number of subjects: 5000 (single arm) Sites throughout entire country were equally listed according the size of the hospitals or general clinics at which Prazaxa® Capsules were available for prescription. Prazaxa® Capsules dose: 300 mg daily (150 mg [as 2 capsules of 75 mg] b.i.d) or 220 mg (110 mg [as 1 capsule of 110 mg] b.i.d). Route of administration: Oral Duration of treatment: 104 weeks		
Subjects and study size, including dropouts:	Main criteria for inclusion Male and female patients with nonvalvular atrial fibrillation who had never been treated with Prazaxa® Capsules / dabigatran etexilate before enrolment.		
Variables and data sources:	Outcomes: Safety Primary Outcome:		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Prazaxa® Capsules			
Name of active ingredient: Dabigatran etexilate			
Report date: 04 July 2017	**Study number:** 1160.130	**Version/Revision:** Version 1.0	**Version/Revision date:** Not applicable

	Incidences of adverse drug reactions Secondary Outcome: Incidences of stroke and systemic embolism Further Outcomes: Incidence of haemorrhage and bleeding Incidence of myocardial infarction Incidence of gastrointestinal disorder Incidences of serious adverse events Others: baseline characteristics Demographics, duration and medical condition of indication, medical history/ concomitant disease, history of bleeding events, concomitant/ past medications and therapy, vital signs and safety laboratory tests, pregnancy Data sources: Patients' data was collected by electronic Case Report Form (eCRF) on Electronic Data Capture (EDC) system
Results:	In this PMS, a total of 6772 patients were registered in Japan. Three-month eCRFs were collected from 6628 patients and 6443 patients included in the safety set, and 6395 patients included in the effectiveness set. More than half of all patients enrolled completed the 2-year follow up (discontinued: 2794 patients, 43.4%). Baseline characteristics Of 6443 patients in the safety set, 4310 (66.9%) patients were male and 2133 (33.1%) patients were female. The mean age was 70.9±9.9 [SD] years, 2728 (42.3%) patients had paroxysmal atrial fibrillation (AF), 1687 (26.2%) patients had persistent AF, 1615 (25.1%) patients had permanent AF, 3 (0.0%) patients had no nonvalvular atrial fibrillation, 969 (15.0%) patients had concomitant gastrointestinal (GI) disorder, 660 (10.2%) patients had concomitant hepatic disorder, 2296 (35.6%) patients had concomitant renal dysfunction and 1063 (16.5%) patients showed lower creatinine clearance (50 mL/min or less). The mean CHADS2 score was

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Prazaxa® Capsules			
Name of active ingredient: Dabigatran etexilate			
Report date: 04 July 2017	**Study number:** 1160.130	**Version/Revision:** Version 1.0	**Version/Revision date:** Not applicable

1.8±1.3 [SD]. The mean CHADS2−VASc score was 3.0±1.6 [SD]. Total of 6231 (96.7%) patients had concomitant use of any drugs, and 870 (13.5%) patients had concomitant use of antiplatelet drugs.

In overall treatments, the mean duration of Prazaxa® treatment was 459.77±292.79 [SD] days, ranged from 1.0 to 1380.0 days. The initial daily dose and number of patients were 4759 (73.86%) for 220 mg, 1571 (24.38%) for 300 mg and 113 (1.75%) for other. The mean maximum daily dose was 239.12±36.61 [SD] mg ranged from 75.0 mg to 440.0 mg.

Primary Outcome

Of 6443 patients, adverse drug reactions (ADRs) were reported for 1818 (28.2%) patients.

At the preferred term level, the most frequent ADRs were dyspepsia (408 patients, 6.3%), activated partial thromboplastin time prolonged (113 patients, 1.8%), hypertension (94 patients, 1.5%), gastrooesophageal reflux disease (80 patients, 1.2%), renal impairment (78 patients, 1.2%) and gastritis (63 patients, 1.0%).

ADRs were reported for 1350 (27.6%) patients treated with 220 mg initial daily dose out of 4898 patients and 413 (25.4%) patients treated with 300 mg initial daily dose out of 1623 patients respectively.

Safety summary

Adverse events (AEs) were reported for 2501 (38.8%) patients in 6443 patients during the course of the PMS study. At the preferred term level, the most frequently reported AEs were dyspepsia (410 patients, 6.4%), hypertension (197 patients, 3.1%), atrial fibrillation (116 patients, 1.8%), activated partial thromboplastin time prolonged (113 patients, 1.8%), renal impairment (102 patients, 1.6%), hyperuricaemia (100 patients, 1.6%), diabetes mellitus, gastrooesophageal reflux disease (86 patients, 1.3% for each), cardiac failure (73 patients, 1.1%), hepatic function abnormal (72 patients, 1.1%), anaemia, blood pressure increased (64 patients, 1.0% for each) and gastritis (63 patients, 1.0%).

The AEs leading to discontinuation of Prazaxa® were reported for 1204 patients in 6443 patients during the course of the PMS study. The most

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Prazaxa® Capsules			
Name of active ingredient: Dabigatran etexilate			
Report date: 04 July 2017	**Study number:** 1160.130	**Version/Revision:** Version 1.0	**Version/Revision date:** Not applicable

frequently reported AEs leading to discontinuation of Prazaxa® at the preferred term level were dyspepsia (295 patients, 24.5%), activated partial thromboplastin time prolonged (94 patients, 7.8%), renal impairment (78 patients, 6.5%), gastritis (38 patients, 3.2%), haematuria (25 patients, 2.1%), abdominal discomfort, gastrooesophageal reflux disease, hepatic function abnormal (24 patients, 2.0% for each), lower gastrointestinal haemorrhage (23 patients, 1.9%), haemorrhage subcutaneous (20 patients, 1.7%), diarrhoea, epistaxis (19 patients, 1.6% for each), cerebral infarction, anemia, gastrointestinal disorder (17 patients, 1.4% for each), abdominal pain (16 patients, 1.3%), nausea, rash (15 patients, 1.2% for each), abdominal pain upper (14 patients, 1.2%), decreased appetite, gastrointestinal haemorrhage, gingival bleeding (13 patients, 1.1% for each) and dizziness (12 patients, 1.0%).

Severe ADRs were reported for 128 (2.0%) patients in 6443 patients during the course of the PMS study. At the preferred term level, severe ADRs reported more than 3 patients were dyspepsia (9 patients, 0.1%), death (8 patients, 0.1%), cerebral infarction (6 patients, 0.1%), cardiac failure, lower gastrointestinal haemorrhage, subdural haematoma (5 patients, 0.1% for each), anaemia, acute myocardial infarction, gastrointestinal haemorrhage and renal impairment (4 patients, 0.1% for each).

Secondary Outcome

In overall patients, the incidence rate of stroke and SEE was 1.27 (95% Confidence Interval (CI) =1.04 to 1.54) per 100 patients year in total, 1.37 (1.11 to 1.71) per 100 patients year at 220 mg, 0.77 (0.46 to 1.28) per 100 patients year at 300 mg, 3.94 (1.64 to 9.46) per 100 patients year at other doses.

Further Outcomes

The incidence rate of any bleeding events was 4.71 (95%CI= 4.26 to 5.21), major bleeding events (according to International Society on Thrombosis and Haemostasis definition) was 1.08 (0.87 to 1.33), minor bleeding events was 3.79 (3.39 to 4.24), ICH was 0.26 (0.17 to 0.40), GI bleeding events was 1.50 (1.26 to 1.79), and other bleeding events (not categorized as ICH or GI bleeding) was 3.13 (2.76 to 3.54) per 100 patients year in total.

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Prazaxa® Capsules			
Name of active ingredient: Dabigatran etexilate			
Report date: 04 July 2017	**Study number:** 1160.130	**Version/Revision:** Version 1.0	**Version/Revision date:** Not applicable
	The incidence rate of MI was 0.15 (95%CI= 0.08 to 0.26) per 100 patients year in total. The incidence rate of GI disorders was 10.49 (95%CI= 9.79 to 11.24) per 100 patients year in total and that of dyspepsia-like/gastritis-like symptoms was 8.02 (7.42 to 8.68) per 100 patients year in total. Serious AEs were reported for 618 (9.6%) patients in 6443 patients during the course of the PMS study. The most frequently reported SAEs at the preferred term level were cardiac failure (73 patients, 1.1%), cerebral infarction (53 patients, 0.8%), cardiac failure congestive (24 patients, 0.4%) and atrial fibrillation (20 patients, 0.3%). Serious ADRs were reported for 262 (4.1%) patients during the course of the PMS study. The most frequent serious ADRs at the preferred term level were all < 1% and as follows: cerebral infarction (24 patients, 0.4%), cardiac failure (20 patients, 0.3%), lower gastrointestinal haemorrhage (12 patients, 0.2%) and subdural haematoma (12 patients, 0.2%).		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Prazaxa® Capsules			
Name of active ingredient: Dabigatran etexilate			
Report date: 04 July 2017	**Study number:** 1160.130	**Version/Revision:** Version 1.0	**Version/Revision date:** Not applicable
Discussion:	Adverse Drug Reactions ADRs including haemorrhage, MI and gastrointestinal disorders were evaluated in the PMS study. However, no remarkable changes were found in major safety profile compared to that obtained at the time of Prazaxa® approval on January 21, 2011. Major risks to enhance the incidence of these ADRs were generally inferred by the precaution stated in the Japanese package insert. Effectiveness (Stroke and Systemic Embolism) From the results for the incidence of stroke and SEE, no notable changes in effectiveness were found for long-term use of Prazaxa® at daily dose of 220 mg or 300 mg from the results which obtained at the time of Prazaxa® approval on January 21, 2011. In addition, there were no notable changes in the incidence of stroke and SEE regardless of assessments for low dose criteria. The results of this Japanese observational, non-interventional study in patients with nonvalvular atrial fibrillation demonstrated that long-term Prazaxa® treatment in clinical practice posed no additional safety issues and supported the long-term effectiveness for stroke and systemic embolism. The safety profile confirmed to the one assessed in the randomized study of RE-LY as described in the Japanese package insert. The study does not indicate any changes on Risk and Benefit concerning with Prazaxa® treatment.		
Marketing Authorisation Holder(s):	Nippon Boehringer Ingelheim Co., Ltd. (NBI) 2-1-1 Osaki, Shinagawa-ku, Tokyo 141-6017, Japan		
Names and affiliations of principal investigators:	Rie Ikeda Phone: +81-(0)3-6417-2200 Post Marketing Surveillance, Pharmacovigilance Department		