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Non-Interventional Study (NIS) Report

Study number: 1160-0284

Document number: c35782212-01

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Prazaxa® Capsules			
Name of active ingredient: Dabigatran etexilate			
Report date: 13 Oct 2021	Study number: 1160-0284	Version/Revision: Version 1.0	Version/Revision date: Not applicable
Title of study:	Post-Marketing Surveillance on the Use of Prazaxa® Capsules in Japanese patients with nonvalvular atrial fibrillation after the availability of idarucizumab.		
Keywords:			
Rationale and background:	The patient population who receive Prazaxa® Capsules and the safety profile of Prazaxa® Capsules is not expected to change after idarucizumab is launched. This study was conducted to investigate the appropriate use of Prazaxa® Capsules in a prospective study after the availability of idarucizumab in the routine medical practice. This post-marketing Surveillance (PMS) study was planned additionally to the requirement by the Act on Pharmaceuticals and Medical Devices (PMD Act) in Japan. The regulatory required PMS (BI trial number: 1160.130) has been completed in January 2017.		
Research question and objectives:	The study objective was to confirm appropriate use and safety profile of Prazaxa® Capsules in Japanese patients with nonvalvular atrial fibrillation in real-world setting after the availability of idarucizumab.		
Study design:	Non-interventional study based on new data collection. The analyses in this PMS were descriptive by nature. No formal statistical inference was made.		
Setting:	Planned number of sites: Approximately 800 Planned number of subjects: 5000 (safety set) Study period: Jul 2017 – Dec 2020 Enrolment period: Jul 2017 – Jun 2019 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. Observation: 4, 8, 12, 26 and 52 weeks after the start of treatment, or at discontinuation.		
Subjects and study size, including	<u>Inclusion criteria</u> Male and female patients with nonvalvular atrial fibrillation (AF) who had		

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dropouts:	never been treated with Prazaxa® Capsules/dabigatran etexilate for preventing the occurrence of ischemic stroke/systemic embolism (SEE) before enrolment. <u>Exclusion criteria</u> None In this PMS, the information on Race and Ethnicity was not collected. The definition of safety set 1 and safety set 2 are as below: - Safety set 1 This patient set included all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment. This patient set included all patients who were documented to take at least one dose of Prazaxa® Capsules except patients who experienced with Prazaxa® Capsules treatment for the prevention of ischemic stroke and SEE, who did not followed registration rules, who registered outside the site contract period and/or who made no visit after the entry. - Safety set 2 This patient set included all patients in the safety set except for patient not diagnosed as nonvalvular AF or in contraindication.		
Variables and data sources:	Outcomes: <u>Primary outcome:</u> Absolute and relative (%) frequency of patients with suspected adverse drug reactions (ADRs). <u>Secondary outcome</u> None <u>Further outcomes:</u> Incidence of stroke/SEE Incidence of bleeding Incidence of myocardial infarction (MI) Incidence of gastrointestinal (GI) disorder		

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		Serious adverse events (SAEs) <u>Others: baseline characteristics</u> 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 status. <u>Data sources:</u> Patients' data was collected by electronic Case Report Form (eCRF) on Electronic Data Capture (EDC) system	
Results:		Several interim analyses were performed for the purpose of submission of periodic safety reports to PMDA in project (status update of using Prazaxa® Capsules not only with this trial but all usage, every 6 month in two years after approval and every 12 months afterward). Interim results was submitted in the re-examination dossier to PMDA on 18 April 2019. The presented results include the outcome of these interim analyses. In this PMS, a total of 5660 patients were registered in Japan. A total of 5565 patients were collected three months eCRFs and 4302 patients were collected twelve months eCRFs (95 patients were not collected eCRF). A total of 3238 patients completed the 12 months study period A total of 5436 patients included in the safety set 1. Of 5565 patients who collected eCRFs, 129 patients were excluded from the safety set 1 due to no actual visit (121 patients), previous treatment experience with Prazaxa® Capsules (5 patients), and registration rule not followed (4 patients). A total of 5362 patients included in the safety set 2 for effectiveness analysis. Of 5565 patients who collected eCRFs, 203 patients were excluded from the safety set 2 due to no actual visit (121 patients), contraindication (46 patients), main diagnosis not met (30 patients), receiving Prazaxa® Capsules treatment before (5 patients), and registration rule not followed (4 patients). The reasons of exclusion from the safety set 1 and the safety set 2 were	

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overlapping. <u>Baseline characteristics</u> Of 5436 patients in the safety set 1, 3812 patients (70.13%) were male and 1624 patients (29.87%) were female. The mean age was 69.8±11.1 [SD] years, 2892 patients (53.20%) had paroxysmal atrial fibrillation (AF), 1474 patients (27.12%) had persistent AF, 743 patients (13.67%) had permanent AF. 304 patients (5.59%) had previous any bleeding, 1268 patients (23.33%) had concomitant cardiac failure, 3500 patients (64.39%) had concomitant hypertension, 1245 patients (22.90%) had concomitant diabetes mellitus, 901 patients (16.57%) had concomitant gastrointestinal (GI) disorder, 383 patients (7.05%) had concomitant hepatic disorder, 1978 patients (36.39%) had concomitant renal dysfunction and 922 patients (16.96%) showed lower creatinine clearance (50 mL/min or less) based on Cockcroft-Gault. The mean CHADS2 score was 1.8±1.3 [SD]. The mean CHADS2-VASc score was 2.9±1.7 [SD]. The mean modified HAS-BLED score was 2.0±1.1 [SD]. Total of 4832 patients (88.89%) had concomitant use of any drugs, and 782 patients (14.39%) had concomitant use of antiplatelet drugs. In the patients of the safety set 1, the mean duration of Prazaxa® Capsules treatment was 287.3±178.8 [SD] days, ranged from 1 to 1114 days. The initial daily dose and number of patients were 3516 (64.68%) for 220 mg, 1898 (34.92%) for 300 mg and 22 (0.40%) for other. The mean maximum daily dose was 248.3±39.3 [SD] mg ranged from 75 mg to 600 mg. <u>Primary outcome</u> Of 5436 patients, ADRs were reported for 581 patients (10.69%). At the preferred term (PT) level coded based on reported from the investigator, the most frequently reported ADRs (>1%) were dyspepsia (67 patients, 1.23%) and abdominal discomfort (55 patients, 1.01%). ADRs were reported for 389 patients (10.77%) treated with 220 mg initial daily dose out of 3612 patients and 167 patients (8.63%) treated with 300 mg initial daily dose out of 1934 patients respectively. <u>Further safety summary</u> Adverse events (AEs) were reported for 1438 patients (26.45%) in 5436 patients during the course of the PMS study. At PT level coded based on			

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		reported term from the investigator, the most frequently reported AEs (>1%) were atrial fibrillation (218 patients, 4.01%), dyspepsia (71 patients, 1.31%), hypertension (65 patients, 1.20%), cardiac failure (64 patients, 1.18%), abdominal discomfort (62 patients, 1.14%). The AEs leading to discontinuation of Prazaxa® Capsules were reported for 652 patients (11.99%) in 5436 patients during the course of the PMS study. The most frequently reported AEs leading to discontinuation of Prazaxa® Capsules at PT level (>1%) were dyspepsia (56 patients, 8.59%), abdominal discomfort (46 patients, 7.06%), nausea (26 patients, 3.99%), renal impairment (25 patients, 3.83%), haematuria (22 patients, 3.37%), cerebral infarction, diarrhoea, melaena, and activated partial thromboplastin time prolonged (15 patients, 2.30% for each), abdominal pain upper and oesophagitis (14 patients, 2.15% for each), cardiac failure and hepatic function abnormal (13 patients, 1.99% for each), gastrointestinal haemorrhage (12 patients, 1.84%), gastrointestinal disorder (11 patients, 1.69%), atrial fibrillation and haemorrhage subcutaneous (10 patients, 1.53% for each), decreased appetite (9 patients, 1.38%), gastritis (8 patients, 1.23%), abdominal pain and dysphagia (7 patients, 1.07% for each). Severe ADRs were reported for 28 patients (0.52%) in 5436 patients during the course of the PMS study. At PT level, severe ADRs reported more than 1 patients were cerebral haemorrhage, dyspepsia, and sudden death (2 patients, 0.04% for each). <u>Further outcomes</u> In the patients of safety set 2 for effectiveness analysis, the incidence rate of stroke/SEE was 1.57 (95% Confidence Interval (CI) =1.21 to 1.99) per 100 patients year. The incidence rates per dose were 1.64 (1.20 to 2.19) per 100 patients year for patients receiving 220 mg, and 1.37 (0.84 to 2.12) per 100 patients year for patients receiving 300 mg. In the patients of safety set 1, the incidence rate of any bleeding events was 4.71 (95% CI: 4.08 to 5.41), major bleeding events (according to International Society on Thrombosis and Haemostasis definition) was 1.08 (0.79 to 1.44), minor bleeding events was 3.80 (3.23 to 4.43), intracerebral haemorrhage (ICH) was 0.30 (0.16 to 0.52), GI bleeding events was 1.53	

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		(1.18 to 1.95), and other bleeding events (not categorised as ICH or GI bleeding) was 3.03 (2.53 to 3.60) per 100 patients year. In the patients of safety set 1, the incidence rate of MI was 0.16 (95% CI: 0.07 to 0.34) per 100 patients year. In the patients of safety set 1, the incidence rate of GI disorders was 7.93 (95% CI: 7.10 to 8.83) per 100 patients year and that of dyspepsia-like/gastritis-like symptoms was 4.69 (4.06 to 5.39) per 100 patients year. In the patients of safety set 1, SAEs were reported for 416 patients (7.65%) in 5436 patients during the course of the PMS study. The most frequently reported SAEs at PT level were cardiac failure 64 patients, 1.18%), cerebral infarction (31 patients, 0.57%), atrial fibrillation (28 patients, 0.52%). In the patients of safety set 1, serious ADRs were reported for 82 patients (1.51%) during the course of the PMS study. The most frequent serious ADRs at PT level were cerebral infarction (13 patients, 0.24%). In the patients of safety set 1, fatal cases were reported for 51 patients (0.94%), and fatal ADRs reported for 10 patients (0.18%). The fatal ADRs reported more than 1 patient were embolic cerebral infarction, death, and sudden death (2 patients, 0.04% for each). <u>Appropriate use of Prazaxa® Capsules</u> Of the 5436 patients of safety set 1, 46 patients (0.83%) were treated with Prazaxa® Capsules as contraindication and 30 patients (0.54%) were "Patient main diagnosis not met".	
Discussion:		<u>Adverse Drug Reactions</u> After the approval of idarucizumab, the patient characteristics and safety profile of those who used Prazaxa® Capsules remained the same as compared to that obtained at the time of Prazaxa® Capsules approval on January 21, 2011. The results of this observational, non-interventional study in Japanese patients with nonvalvular AF after the availability of idarucizumab showed	

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	that Prazaxa® Capsules treatment in clinical practice posed no additional safety issues after idarucizumab was launched. The study does not indicate any changes on Risk and Benefit concerning with Prazaxa® Capsules treatment.		
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