1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa®			
Name of active ingredient: ACT code B01AE07 Dabigatran etexilate			
Report date: 14 December 2016	**Study number:** 1160.162	**Version/Revision:** Version 1.0	**Version/Revision date:**
Title of study:	An observational study assessing the management of gastrointestinal and urogenital bleeding events in patients with non valvular atrial fibrillation treated with dabigatran etexilate		
Keywords:	Chart review study, management of gastrointestinal and urogenital bleeding events, dabigatran etexilate, non valvular atrial fibrillation		
Rationale and background:	Dabigatran etexilate has been approved in more than 100 countries for stroke prevention in atrial fibrillation (AF) based on significant clinical benefits seen in the Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate (RE-LY) trial. Compared with well-managed warfarin (target international normalized ratio [INR] of 2–3; median time in therapeutic range [TTR] of 67.3%), dabigatran 150 mg and 110 mg taken twice daily demonstrated superior stroke reduction and non-inferior stroke prevention, respectively. Incidences of major bleeding were similar in patients treated with dabigatran 150 mg twice daily and warfarin, while bleeding events were less frequent in patients treated with dabigatran 110 mg twice daily. Furthermore, as demonstrated in an analysis by Majeed et al. [P13-12677] using data from five phase III trials of dabigatran for stroke prevention in AF and treatment for venous thromboembolism (VTE), the overall resources required to manage bleeding were not greater, and the prognosis after a major bleeding was not worse in patients on dabigatran compared to those on warfarin. This study was aimed to retrospectively assess the management of specific types of bleeding in patients who used dabigatran in a real-world setting.		
Research question and objectives:	The objective of this observational study is to assess the clinical characteristics of the gastrointestinal (GI) and urogenital (GU) bleeding events in patients with non valvular AF taking dabigatran who present to emergency departments/rooms (EDs/ERs) for management of such events, and additionally to collect information describing the diagnostic evaluations and treatments provided to resolve these events, and the clinical outcomes of these events.		
Study design:	Observational chart review study		
Setting:	Clinical sites from varying geographical regions in the United States (US) and Canada that treated patients with non valvular AF who		

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	received dabigatran were selected for study inclusion. Patients who presented to the ED/ER (index visit) with an acute GI and/or GU bleeding event (index event) at one of the participating study sites between October 28, 2010 and August 1, 2013 (eligibility period) were included in the chart review. The study period for data collection for each patient is defined as the period between the date of index visit and the date of discharge from the ED/ER (index discharge), the observation unit or inpatient hospitalization. For the few patients who had a revisit, details of the management of the events and use of dabigatran were abstracted from patients' medical charts as well.		
Subjects and study size, including dropouts:	Patients who satisfied the following eligibility criteria were included in the chart review: ***Inclusion criteria*** • Adult patients ≥ 18 years of age; • Confirmed diagnosis of non valvular AF; Documentation of presentation to an ED/ER for an acute GI and/or GU bleeding event (index event) between October 28, 2010 and August 21, 2013; • Documentation that the index event occurred in a patient who reported having taken at least one dose of dabigatran within the 5 days prior to the index event. ***Exclusion criteria*** • Confirmed diagnosis of valvular AF; • Documentation that the patient was taking dabigatran with a concomitant anticoagulant (contemporaneous parenteral anticoagulant or another oral anticoagulant) within 72 hours prior to the onset of the index event; o The concomitant administration of antiplatelet medications prior to the onset of the index event is not exclusionary • Documentation of the patient receiving thrombolytic therapy within 48 hours prior to the onset of the index event; • Documentation that the patient was enrolled in an investigational clinical trial at the time of onset of the index		

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	event; • Medical record was not retrievable, was missing or empty. Overall, 44 sites (12 sites from Canada and 32 sites from the US) participated, and site staff reviewed the medical charts of 220 unique patients (Canada: 75 patients, US: 145 patients) for study data collection.
Variables and data sources:	Data on demographics, medical history, use of dabigatran and management of GI and/or GU bleeding events were collected from patients' medical charts. The primary study variables were: • Outcome of the bleeding events at the time of discharge: o Ongoing, if symptoms of bleeding not completely resolved at time of discharge; o Deceased in case of death; o Resolved otherwise • Type of interventions used to treat bleeding events in the ED/ER setting • Type and anatomic location of the index event Other study variables include documented use of concomitant medications taken within 30 days prior to the index event and/or during the study period. In particular, for concomitant medications taken after the index event, investigators had to specify whether these medications were used as treatments for the index event.
Results:	Site staff from 44 clinical sites collected data from the medical charts of 220 patients. The mean age of patients was 76.1 years (SD: 10.3) and 108 were female (49%). Of patients with known date of AF diagnosis (n=119), 99 (83.2%) were diagnosed with AF ≥6 months prior to ED/ER visits for the index bleeding events. Eighty-four (84) patients (38.3%) were taking one or more medications known to increase the risk of bleeding within 5 days prior to ED presentation. Anatomic locations of the bleeds are described below by type of bleeding event; bleeding appearing in multiple locations was possible: n=4 patients (1.8%) had both GI and GU bleeding. • GI bleeding: n=161 (73.2%) o Upper GI bleeds: 34 (15.5%)

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- Lower GI bleeds: 101 (45.9%)
- Location unknown: 28 (12.7%)

- GU bleeding: n=63 (28.6%)

Per study eligibility, all patients received at least one dose of dabigatran within the 5 days prior to the index visit. The last dabigatran dose prior to the index event, as reported in the chart, was 150 mg for 129 patients (58.7%), 110 mg for 44 patients (20.0%) (Canada only), 75 mg for 19 patients (8.6%), and unknown for 19 patients (8.6%). In addition, 300 mg was documented in the charts of the remaining 9 patients; however, it was not indicated whether this was the total daily dose or the last dose ingested by the patient.

Overall, 127 patients had 228 diagnostic and evaluation procedures during their index visits, including endoscopy (n=50, 21.9%), colonoscopy (n=49, 21.5%), and fecal occult blood test (FOBT)/digital rectal exam (DRE) (n=43, 18.9%).

For most patients (n=170, 77.3%), at least one intervention was documented in the charts, while 50 patients (22.7%) received no intervention to treat their bleeding events. The most common intervention was discontinuation of dabigatran (n=157, 71.4%) followed by transfusion/infusion (n=81, 36.8%, predominantly packed red blood cell transfusions: n=60/81, 74.1%). Thirty (30, 13.6%) patients had medications documented in their medical record considered to have been used to treat the bleeding event. Those medications included proton pump inhibitors (PPIs, 25 patients, all with GI bleed), vitamin K (n=7), H2 antagonists (n=1), and factor concentrate (n=1). Surgery was reported for 15 patients (6.8%) and therapeutic procedures (e.g., colonoscopy) for 21 patients (9.5%).

The mean duration of index visit was 7.6 hours (SD: 8.5). One-hundred and forty-eight (67.3%) patients were admitted to the hospital with a mean duration of stay of 5.7 days (SD: 6.6). Fourteen patients had a revisit beyond 7 days following the index discharge.

At the time of index discharge, 169 (76.8%) patients had their bleeding events resolved, 42 patients still had some symptoms of bleeding and their bleeding was classified as ongoing (19.1%), 9 (4.1%) patients had died. Primary causes of death were index event (n=1), sepsis (n=2), congestive heart failure (n=2), cancer (n=1), cardiac arrest (n=2), and

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	ischemic bowel (n=1). As specified in the protocol, all adverse events, including the index GI/GU bleeding event leading to the enrolment of the patient, were considered. Overall, 651 adverse events (AEs) were documented in the medical charts for the 220 patients. Of those, 395 were considered serious, occurring in 184 patients (83.6%), while the remaining 256 were considered non-serious, occurring in 136 patients (61.8%). Eleven patients (5.0%) had 14 fatal adverse events; 9 died during the index hospitalisation and 2 died beyond the end of individual patient's study period but before date of site close-out dates.		
Discussion:	Large phase III trials evaluating dabigatran compared to warfarin have allowed the description of the management of major bleeding events and associated outcomes before the availability of the dabigatran reversal agent, idarucizumab [P13-12677, P16-02382]. In these analyses based on 1,034 patients (627 exposed to dabigatran), bleeding in patients receiving dabigatran was managed with comparable or superior effectiveness and lower 30-day mortality rates, as compared to bleeding in patients receiving warfarin. This chart abstraction, observational study aimed to characterize GI and GU bleeding events in patients with non valvular AF taking dabigatran in a real-world clinical setting. It therefore complements the data available from the phase III trials for a different population. The sample size (220 patients) and availability of data in the patients' ED/ER medical charts do not allow for either conclusions on the appropriateness of the measures taken to manage the bleeding events or for the assessment of their effectiveness. There is limited clinical knowledge to characterize the bleeding events and the rationale for treatment. However, it provides first insights into the characteristics of patients in the real-world setting in North America and on the treatment approaches prior to idarucizumab availability.		
Marketing Authorisation Holder(s):	Boehringer Ingelheim		
Names and affiliations of principal investigators:	Twenty-two investigators (6 from Canada and 16 from the US). [redacted]		