Title: Xarelto (Rivaroxaban) Risk Minimisation Plan Evaluation: Patient and Physician Knowledge of Key Safety Messages

Progress Report - EUPAS3911

This PASS category-3 study is being conducted by RTI Health Solutions, a member of the ENCePP, with assistance of Kantar Health for field operations.

This study serves to evaluate additional risk minimization measures as outlined in the EU RMP for rivaroxaban, with regard to approved indications (venous indications and SPAF). As part of the EU RMP, additional risk minimization tools were developed that included a Prescriber's Guide (PG) and Patient Alert Card (PAC), with the aim to increase awareness and understanding among physicians and patients about the potential bleeding risk during treatment with rivaroxaban. Per agreement with the EMA, a study protocol was designed in order to test these elements of the EU RMP. Evaluation surveys were planned for administration in 3 waves at 18 months, 3 years, and 7 years post launch, and the status of these assessments to be presented regularly in PBRERs.

The first wave of the study surveys has been completed in October 2015. An interim report on wave 1 survey was submitted to EMA on 08 DEC 2015 (PAM [MEA] 023.2). On 21 JUL 2016, EMA has endorsed the MAH's proposal (submitted 22 APR 2016) to amend the study protocol to omit patients from the following surveys (waves 2 and 3). The wave 2 of physician surveys has been completed and an interim report was submitted to EMA on 13 JUN 2018. On 20 SEP 2018, after the data lock point of this PBRER, the respective Assessment Report (PAM [MEA] 023.4) was adopted by the CHMP. It was acknowledged that the study met its objectives in (a) evaluating whether physicians received the educational materials (i.e. Prescriber's Guide [PG]) for Xarelto) and (b) assessing physicians' knowledge and understanding of key safety information as well as use of the materials, thus the PAM (all commitments for the wave 2 report) has been fulfilled. The MAH should address, within the next upcoming revision of the prescriber guide, whether there is a need for clarification of the information on posology to further aid the prescribers and endeavor to ensure that the prescriber guide is available to all prescribing physicians.

In summary, the number of completed physician surveys included 304 surveys each from France and Germany, 308 from Spain, and 310 from the UK for a total of 1 226. The overall evaluable response rate was 6%. In general, physicians' knowledge of the key safety information in the Xarelto educational materials was high and consistent with results observed in wave 1. Physicians' knowledge was particularly high for questions related to the risk of bleeding (94%), populations that are at increased risk of serious side effects (69%-94%), and contraindications (73%-92%). Physician knowledge was also high for questions related to invasive procedures (80%) and medically important bleeding (59%-81%). Fewer physicians (62%) were aware that rivaroxaban (15 mg or 20 mg) should be taken with food for stroke prevention in atrial fibrillation (SPAF) and deep vein thrombosis (DVT) treatment and secondary prevention. Knowledge was lower for situations that require international normalised ratio monitoring (58%-76%), procedures for converting from vitamin K antagonist (VKA) to rivaroxaban (52%-66%) and from rivaroxaban to VKA (36% 62%), and for converting from parenteral anticoagulants to rivaroxaban (51% 54%). In conclusion, physicians' knowledge was highest for the most important risks and lower for more complex aspects

of safe use for which it is assumed that physicians would consult the prescriber guide and/or label rather than relying on memory.

Study finalization is estimated for 2020.