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October 20, 2011

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Dear Drs. Woodcock and Stockbridge,

These comments from Public Citizen's Health Research Group are being sent in response to New Drug Application (NDA) #202439, submitted by Johnson & Johnson Pharmaceutical Research and Development, LLC, on behalf of Ortho-McNeil-Janssen-Pharmaceuticals and considered by the Food and Drug Administration's (FDA) Cardiovascular and Renal Drugs Advisory Committee on September 8, 2011, for rivaroxaban (Xarelto) for the prevention of stroke and non-central nervous system (CNS) systemic embolism in patients with nonvalvular atrial fibrillation:

We strongly oppose FDA approval of Johnson & Johnson's NDA for rivaroxaban for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, a condition for which two proven therapies already exist. The phase 3 ROCKET trial conducted in support of the proposed indication had a suboptimal control arm, showed a possible rebound excess in stroke occurrence following rivaroxaban discontinuation, tested only one dose of the study drug with no rationale as to why the chosen dose was used, and involved ethical concerns related to study protocol and conduct.

Background and overview

Rivaroxaban, an oral anticoagulant that acts by directly inhibiting Factor Xa, was approved by the FDA in July 2011 for the prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing knee- or hip-replacement surgery.¹ Two months later, the FDA's Cardiovascular and Renal Drugs Advisory Committee was convened to discuss a new indication "for the prevention of stroke and systemic embolism (blood clots other than in the head) in patients with non-valvular atrial fibrillation."² The evidence for the proposed indication was based on the large, global, randomized phase 3 ROCKET trial comparing rivaroxaban with warfarin in patients with atrial fibrillation at high-risk for ischemic stroke or systemic embolism.³

At the conclusion of its September 8 meeting, the FDA's Cardiovascular and Renal Drugs Advisory Committee recommended approval of rivaroxaban for the prevention of stroke and systemic embolism in patients with chronic atrial fibrillation. The committee came to that decision despite the opinion of the FDA's three clinical reviewers (Nhi Beasley, Preston Dunnmon [safety], and Martin Rose [efficacy]; hereafter referred to simply as "FDA reviewers" or "reviewers") that rivaroxaban should not be approved unless the manufacturer conducts further studies to support the efficacy and safety of rivaroxaban over appropriately-managed warfarin therapy, and despite the serious reservations expressed by some of the committee members themselves.

Tom Fleming, an epidemiologist and frequent consultant to the FDA, and a member of the advisory committee that met in September of this year, recently published an article in *The New England Journal of Medicine (NEJM)* in which he highlighted these reservations.⁴ Regarding the outstanding safety concerns, Dr. Fleming explained that some members voting affirmatively did so even as they recognized that there were still unanswered questions, which they were relying on postmarketing trials to resolve:

"Justification [for voting to approve the indication included] ... the expectation that evidence can be obtained to establish that risk will be reduced by short-term continuation of rivaroxaban when transitioning to other anticoagulant therapy [and] the belief that postmarketing studies can address FDA concerns that a twice-daily dosing regimen is more appropriate."

It also appears that at least some members voting to approve rivaroxaban for this condition did so despite implicitly concluding that the drug may not be as safe or effective as the two existing therapies, warfarin and dabigatran (Pradaxa; Boehringer Ingelheim), proposing that it be approved but restricted for use as a third-line treatment. According to Dr. Fleming:

“It was suggested that rivaroxaban might be used in patients who have an inadequate response to or cannot take dabigatran or warfarin, although data are not available to directly address rivaroxaban’s efficacy and risks in such settings.”

These concerns, and others, were addressed in the detailed analysis conducted by the FDA reviewers, who recommended against approval. Although rivaroxaban was shown to be non-inferior to warfarin *as used in the study*, the reviewers noted three major reservations with the ROCKET trial that cast considerable doubt on whether rivaroxaban is truly as safe and effective as warfarin in the prevention of stroke in patients with atrial fibrillation:

1. **Suboptimal use of warfarin in the control group.** In the ROCKET trial, patients in the warfarin arm did not achieve the full benefit of warfarin, compared to usage in all other warfarin-controlled trials of anticoagulants. Time in therapeutic range (TTR) is used commonly to measure optimal warfarin compliance in studies with a warfarin arm. The TTR refers to the percentage of study days in which adequate anticoagulation is achieved with warfarin, “adequate anticoagulation” being defined as an International Normalized Ratio (INR) of 2.0-3.0 in patients with chronic atrial fibrillation. In ROCKET, the mean overall TTR in the warfarin arm was 55%, whereas TTR in all other modern warfarin-controlled studies of anticoagulants ranged from 63% to 73%.⁵ Therefore, rivaroxaban was being compared to suboptimal warfarin therapy, leading the FDA reviewers to conclude that “rivaroxaban should not be approved unless the sponsor submits convincing information that it is as safe and effective for its target indication as warfarin when it is used skillfully.”⁶

At those study sites where warfarin was used skillfully (i.e., when mean TTR exceeded 68%), there was a higher number of strokes and systemic emboli in the rivaroxaban arm, but the imprecision of the estimates due to the smaller sample sizes precluded any conclusions. The reviewers concluded that this uncertainty in the estimates of rivaroxaban’s efficacy “argues strongly for the need for additional data to support approval.”⁷ We agree with the FDA reviewers that the ROCKET trial is insufficient to support approval of rivaroxaban for this indication and that another clinical study must first be performed in which warfarin is used at least as skillfully and appropriately as it has been in all prior warfarin-controlled anticoagulant trials.

2. **Rebound excess in strokes after discontinuation of rivaroxaban.** In the ROCKET study, there was an excess of strokes in the rivaroxaban arm during the transition from blinded study drug to open-label warfarin at the end of the study.⁸ This may be due to the fact that the sponsors did not include a “warfarin

bridge” (i.e., keeping patients on rivaroxaban until INR was therapeutic, usually a period of a few days) when transitioning the patients to warfarin after the study’s end. Although the sponsor belatedly provided a suggested protocol for transitioning patients off rivaroxaban to warfarin, the protocol has not been tested for efficacy or safety in any atrial fibrillation study and does not seem to be based on anything but the sponsor’s conjecture. In addition, an analysis of data from both the ROCKET trial and the RECORD trials (the phase 3 trials conducted in support of rivaroxaban’s original indication for DVT and PE prophylaxis in knee- and hip-replacement patients) suggests a possible rebound hypercoagulable state induced following rivaroxaban withdrawal.

We therefore urge that the following analyses be performed as part of the *preapproval* clinical study recommended above: 1) a pre-specified analysis confirming the safety and efficacy of the proposed instructions to transition patients from rivaroxaban to warfarin and 2) pharmacokinetic and clinical analyses confirming that discontinuation of rivaroxaban does not induce a temporary hypercoagulable state.

3. **Lack of adequate dosing studies.** The sponsor tested only one dose (20 milligrams [mg] once daily) in the ROCKET trial. However, evidence from phase 2 trials indicated that twice-daily dosing (10-mg bid) may be safer than the chosen dose (20 mg once daily) in ROCKET. The FDA reviewers wondered why the sponsor chose to test only one dose, and one reviewer recommended that “the sponsor must perform a clinical study to evaluate the efficacy and safety of a lower dose and/or additional dosing regimens, including at least one [twice-daily] regimen, before this product is approved.”⁹ We agree that such a study must be performed *prior to approval* to ensure that the tested dose is in fact the optimal dose.

4. **Ethical issues surrounding: 1) the discontinuation of the study drug at the end of the treatment period, and 2) substandard therapy in the warfarin arm, especially at international sites.** In addition to the three main objections raised by the FDA reviewers above, there are two potential ethical concerns related to the design and conduct of the ROCKET trial. Despite the fact that, according to the reviewers, “essentially all patients” in this high-risk study population should have received anticoagulation at all times,¹⁰ the study protocol did not mandate anticoagulation or even a formal evaluation for consideration of anticoagulation in the 30-day period after study-drug discontinuation. Over 40% of patients discontinuing the study early, and 7.8% of those completing the study, were followed for 30 days with no anticoagulation administered.

Furthermore, patients, particularly those at international study sites (Table 2), were insufficiently treated with a standard therapy (warfarin) throughout the trial, with no indication that the sponsor intervened at any point to address this dangerous situation. Failing to ensure that patients receive adequate therapy, particularly in cases involving life-threatening outcomes, during a clinical trial is clearly unacceptable.

We discuss each of these four concerns in detail below.

Suboptimal use of warfarin in the ROCKET trial

The uncertainties surrounding the optimal use of warfarin in the ROCKET trial were not seen with the phase 3 trial of another recently approved drug, dabigatran. Dabigatran was approved in October 2010 for the prevention of strokes in patients with atrial fibrillation, an approval based on the phase 3 trial RELY, which showed that the drug was non-inferior to warfarin for this indication.¹¹ In contrast to the ROCKET study, warfarin was used optimally in patients in the control group, with a mean TTR of 63.4-64.4%,¹² with half of study participants at centers with TTR of 67% or greater.¹³ Therefore, dabigatran was shown to be as effective as warfarin used appropriately.

The same cannot be said of rivaroxaban. In ROCKET, the study protocol mandated that the dose of warfarin be titrated to an INR target of 2.5, with a range of 2.0-3.0. However, unlike in RELY and other previous warfarin-controlled trials, no dosing algorithm or guideline was provided. The sponsor instead relied entirely on investigators' clinical judgment as to how to dose warfarin to attain and then maintain INR within the target range.¹⁴ This lack of a systematic protocol to ensure patients were kept within a narrow therapeutic range is alarming, considering the sharp increase in thrombotic and bleeding complications incurred with even small deviations from this range. The reliance on clinical judgment instead of systematic dosing guidelines, according to the FDA reviewers, may have been responsible for the suboptimal therapy received by warfarin patients in the trial:

“The blinding procedures on their face seem appropriately rigorous. However, the lack of a standardized algorithm for maintenance warfarin dose adjustment may have contributed to the overall mediocre TTR for INR in this study.”¹⁵ [emphasis added]

Historically, among all other recent warfarin-controlled clinical trials of anticoagulants, the TTR for patients getting warfarin has ranged from 62% to 73%, considerably higher than the ROCKET TTR of 55% (Table 1).¹⁶ Of the 45% of study time outside of the therapeutic INR range (2.0-3.0), twice as much time (29%) was spent below 2.0 than above 3.0 (14%).¹⁷ This would naturally expose more warfarin patients to ischemic

strokes, which would make rivaroxaban falsely appear to be relatively superior in terms of stroke prevention.

Table 1. Mean INR Time in Therapeutic Range (TTR) in Recent Trials Using Warfarin as Control (taken as-is from FDA backup slides¹⁸)

Trial	Mean TTR
ROCKET	55
ACTIVE W	64
AMADEUS	63
ARISTOTLE	62
EMBRACE AC	73
RELY	64
SPORTIF III	66
SPORTIF V	68

Post-hoc analyses were conducted based on study time spent below INR of 2.0 (and discounting time spent above INR of 3.0, as the rate of ischemic strokes — the most common end point — does not *decrease* substantially above this level, while the rate does *increase* steeply at INRs below 2.0). With an increased percentage of time spent below INR 2.0, there would be more ischemic strokes in patients on warfarin, thus making rivaroxaban seem relatively more effective and reducing the hazard ratio of rivaroxaban. This was confirmed, as sites with the greatest amount of time below the therapeutic range (TBTR > 38%) had the lowest hazard ratio, at 0.73 (95% CI: 0.49, 1.07), increasing progressively with each decrease in TBTR, up to 0.91 (95% CI: 0.59, 1.41) at the sites with the least time (TBTR < 19%) with INR <2.0 (no trend p-values reported).

Given that the main end point, ischemic stroke, is most increased in the warfarin arm when warfarin is used subtherapeutically (e.g., TBTR >38%), then rivaroxaban might actually be inferior when warfarin was used therapeutically or supratherapeutically, which it was not. At sites where warfarin patients spent the least amount of time (<19%) below INR 2.0, rivaroxaban was still non-inferior to warfarin (95% CI crosses one at all sites, regardless of the time spent below the INR). However, given 1) the diminished power inherent in such subgroup analyses to find a difference in event rates between the arms and 2) the progressive increase in hazard ratios with decreasing time spent below INR 2.0, the fact that there were no good data available on “very good” warfarin control (i.e., intervals lower than 19% of time below INR 2.0) was concerning to the reviewers:

“Subgroups with lower rates of TBTR would be expected to have higher hazard ratios. The data from this analysis suggest that at sites where control of INR is very good, treatment with rivaroxaban may not be as effective as treatment with warfarin.”¹⁹

Thus, although rivaroxaban was shown to be non-inferior to warfarin at all quartiles of TBTR, the analysis was post hoc and may not have had sufficient power in each of the quartiles to identify a significant difference in event rates. This trend reinforces the need for an adequately powered clinical study to verify that rivaroxaban is as effective as warfarin at all levels of skillful warfarin use.

In addition, the TTR of 55% is relatively low even when compared with real-world control. Two meta-analyses have been conducted by Dolan et al (2008, of various anticoagulants but most commonly warfarin) and Baker et al (2009, of warfarin) of all studies measuring TTR in atrial fibrillation patients in primary care and specialty clinics.^{20,21} Dolan et al found a mean TTR of 61.3% (95% CI: 58.8, 63.8) with a numerically, but not significantly, higher rate of control in those whose INR was more frequently monitored (**mean TTR 64.3%**; 95% CI: 60.5, 68.0) than those infrequently monitored (mean TTR 59.1%; 95% CI: 55.5, 62.8). Although Baker et al found a mean TTR identical to that from the ROCKET trial, 55% (95% CI: 51, 58), they found significantly better warfarin control in patients in anticoagulation clinics (**mean TTR 63%**; 95% CI: 58, 68) than those in primary care (mean TTR 51%; 95% CI: 47, 55). Thus, studies of warfarin control in practice found that when warfarin use was managed rigorously (as in specialty clinics or with frequent monitoring), TTR was consistently higher than that achieved in the ROCKET trial, a controlled study where patients were similarly closely followed.

Rebound excess of strokes occurred following rivaroxaban discontinuation

As noted above, there was an excess of primary end point events (composite of stroke and non-CNS systemic embolism) in rivaroxaban-treated patients in the three to 30 days after discontinuation of the blinded study drug. There were a total of 22 such events in the rivaroxaban arm compared with six events in the warfarin arm (HR 3.72; 95% CI: 1.51, 9.16). All of the events were strokes, the majority of which (18 of 22 and four of six in the rivaroxaban and warfarin arms, respectively) were ischemic strokes (HR 4.56; 95% CI: 1.54, 13.5).²²

The highest rate of strokes occurred three to seven days after the last dose of study drug administered.²³ This is consistent with the pharmacokinetics of both warfarin and rivaroxaban. Rivaroxaban has a half-life of anywhere from five to 13 hours and is therefore subtherapeutic beginning one day after discontinuation. Warfarin, as is well

known, does not achieve therapeutic levels for a few days after the first dose and may even act as a pro-coagulant prior to achieving therapeutic levels (INR of 2.0), due to the earlier inhibition of vitamin K-dependent anti-clotting factors.²⁴ For this reason, heparin or another rapid-onset anticoagulant (referred to as “bridge” therapy) is often given for the first few days of warfarin therapy to serve as an effective anticoagulant until warfarin achieves full efficacy. In ROCKET, only 1% of rivaroxaban-treated patients were started on open-label warfarin or other vitamin K antagonist (VKA) therapy prior to the last dose of rivaroxaban.²⁵ The vast majority (88%) began anticoagulation in days 0-2 following rivaroxaban discontinuation.²⁶ Therefore, given the five-day delay for warfarin to start working, most patients taken off rivaroxaban had essentially no effective anticoagulation for the first five to seven days off therapy, consistent with the finding that the highest rate of strokes occurred three to seven days after the last dose of rivaroxaban. The reviewers concluded:

“These data suggests [sic] that the completers who had events in this period simply may have been a high risk group with a low tolerance for inadequate anticoagulation. Rivaroxaban arm patients may [have] been at greater risk than those in the warfarin arm simply because of the short half-life of rivaroxaban’s PD effect compared to warfarin, which could have increased the degree and duration of inadequate anticoagulation in the rivaroxaban arm.”²⁷

If this is true, then the rebound excess in strokes may be addressed in practice by simply beginning warfarin prior to discontinuation of rivaroxaban. However, the sponsor had no such protocol in place for investigators prior to the study’s completion. The reviewers noted this stark omission and its association with the excess in strokes in the rivaroxaban arm:

“The lack of direction in the protocol regarding how to transition the study patients off of study drug was associated with a sharp increase in the rate of stroke in rivaroxaban patients.”²⁸

After the study was completed, the sponsor belatedly provided to the FDA a suggested protocol for bridging patients off rivaroxaban to other anticoagulation, instructing providers to initiate warfarin therapy prior to discontinuing rivaroxaban and continuing rivaroxaban until the INR was higher than 2.0.²⁹ However, the instructions were not based on any clinical evidence of their efficacy or safety.

In addition, the sponsor did not provide patient pharmacokinetic data to reassure FDA reviewers that the excess in strokes following discontinuation was not due to rebound pro-coagulant effects.³⁰ In fact, one analysis submitted at the FDA’s request raises the possibility that this may be the case.³¹ The analysis first computed the rate of occurrence of the primary end point (composite of stroke and non-CNS systemic

embolism) in the first 30 days of warfarin therapy in patients in the warfarin arm who were VKA-naïve. This rate was then compared to that seen in rivaroxaban-treated patients (presumably also VKA-naïve, 92% of whom were transitioned to VKA therapy) during the 30 days after treatment discontinuation. Similar event rates would confirm that the excess in strokes seen in rivaroxaban-treated patients after discontinuation were simply due to inadequate anticoagulation. However, event rates in rivaroxaban-treated patients were 6.42 per hundred patient-years, 1.72-fold higher than the rate seen in the warfarin-treated patients (3.78 per hundred patient-years). Although no definitive conclusion can be reached from this post hoc analysis, this disparity in event rates suggests that rivaroxaban may induce a hypercoagulable state following discontinuation. The reviewers concluded:

“These data do not allay our concerns about the possible existence of a hypercoagulable state in patients who discontinue from chronic rivaroxaban therapy.”³²

Furthermore, the same concern for a rebound hypercoagulable state was seen in the phase 3 RECORD trials conducted to support rivaroxaban’s original indication of prevention of DVT and PE in knee- and hip-replacement surgery patients.³³ Unlike in ROCKET, rivaroxaban was given only for short-term prophylaxis (up to 14-35 days after surgery) in the RECORD trials. However, as in ROCKET, patients were not required to be transitioned to alternative anticoagulation while being followed after the end of the study. Following study-drug discontinuation, six (0.10%) patients in the rivaroxaban group had ischemic strokes compared to one (0.02%) patient in the enoxaparin group. Cardiovascular events also occurred earlier after rivaroxaban discontinuation than enoxaparin discontinuation. Of a total of 17 (0.28%) cardiovascular events in the rivaroxaban group and 14 (0.23%) in the enoxaparin group, 11 (66%) events (four myocardial infarctions, three strokes, and 4 cardiovascular deaths) in the rivaroxaban group compared to two (14%) events (one cardiovascular death and one unexplained death) in the enoxaparin group occurred within 10 days after the last dose of treatment. Seven (41%) events (two myocardial infarctions, two strokes, and three cardiovascular deaths) in the rivaroxaban group compared to one (7%) event (cardiovascular death) in the enoxaparin group occurred within five days after the last dose of treatment. The FDA medical reviewers concluded:

“The earlier occurrence of cardiovascular events and a higher incidence of ischemic stroke during off-treatment [in rivaroxaban-treated patients] raise concerns of possible rebound effect for rivaroxaban after the treatment is withdrawn.”³⁴

Therefore, although the exact cause of the excess in strokes may indeed be due to inadequate anticoagulation provided by trial investigators following rivaroxaban

discontinuation, a rebound hypercoagulable state cannot be ruled out based on both the RECORD and ROCKET trials. In neither trial did the sponsors provide pharmacokinetic data to reassure reviewers of the absence of such an effect, and one post hoc analysis in the ROCKET trial found an excess of stroke occurrence beyond that expected when compared with a similar warfarin-treated population.

Only a single, once-daily dose tested despite data supporting twice-daily dosing

It is unclear how only one (20-mg once-daily) dose for this indication was decided upon for ROCKET, and the sponsor never provided sufficient rationale for its chosen dose. According to the reviewers, both the phase 2 trials to determine safety and efficacy of rivaroxaban for its original indication (prevention of DVT in patients undergoing hip and knee replacement) and the phase 2 trials (not further pursued) of rivaroxaban in patients with recent acute coronary syndrome (ACS) showed that:

“[twice daily] dosing may have a better benefit/risk profile than once daily dosing at the same TDD [total daily dose].”³⁵

This conclusion was based on the fact that in the DVT prevention study, the 20-mg twice-daily dose was numerically more effective (significance levels not reported) than the 40-mg once-daily dose.³⁶ Due to this observation, the FDA asked the sponsor to “provide [its] rationale for a once daily dosing regimen” prior to the ROCKET trial. The sponsor did not provide the requested information to “allay [the FDA’s] concerns.”³⁷

The safety data for the ACS phase 2 trials also raised the possibility that a twice-daily dosing schedule may be preferable. A consistent dose-response effect was seen with clinically significant bleeding rates, with increased doses of rivaroxaban associated with increased bleeding rates at almost all doses.³⁸ In addition, for the 20-mg total daily dose, twice-daily dosing resulted in numerically lower bleeding rates than once-daily dosing across all strata.

The choice of once-daily over twice-daily dosing raises questions as to whether the sponsor deliberately chose the once-daily dose in order to ensure a marketing edge with more convenient dosing if approved. As Dr. Fleming noted in the *NEJM* article published this month:

“If the apparent noninferiority of once-daily rivaroxaban to warfarin was due primarily to a low time in therapeutic range in the warfarin group and the exclusion of excess events after randomized treatment was discontinued, then that dosing strategy might be unacceptably inferior to dabigatran. **These circumstances could lead to an unproven treatment displacing an effective**

treatment [dabigatran] on the basis of overzealous promotion of more convenient once-daily dosing.³⁹ [emphasis added]

Of course, we do not know whether the as-yet unjustified choice to pursue ROCKET using only a single, once-daily dose of rivaroxaban was a deliberate attempt by the sponsor to out-compete twice-daily dabigatran. Regardless of the sponsor's motivations, however, Dr. Fleming's point remains valid. Once approved, rivaroxaban's more convenient dosing regimen will undoubtedly be highlighted in promotional campaigns as superior to dabigatran's twice-daily dosing and warfarin's once-daily but frequently monitored dosing.

Therefore, there is uncertainty in, and no clear reasoning for, choosing a single, 20-mg once-daily dose in the ROCKET trial. The sponsor has not provided the rationale for this decision, and we agree with the reviewers that "the sponsor must perform a clinical study to evaluate the efficacy and safety of a lower dose and/or additional dosing regimens, including at least one [twice daily] regimen, before this product is approved."⁴⁰

Ethical issues surrounding: 1) the discontinuation of the study drug at the end of the treatment period, and 2) substandard therapy in the warfarin arm, especially at international sites

In addition to the three main objections above raised by the reviewers, there are two potential ethical concerns related to the conduct of the ROCKET trial. As mentioned above, the high-risk study population chosen for the ROCKET trial was unique among warfarin-controlled anticoagulant trials.⁴¹ The FDA reviewers observed that:

"...all study patients (except a trivial number of protocol violators) had a CHADS2 score of at least 2 at entry, 87% had a CHADS2 score of 3 or more, and about 55% had a prior history of stroke, TIA, or systemic embolism. **Essentially all patients should have ... received anticoagulant therapy if US guidelines had been followed.**"⁴² [emphasis added]

Yet the study protocol did not mandate anticoagulation or even a formal evaluation for consideration of anticoagulation in the 30-day period after drug discontinuation. In the one-third of patients who terminated the study early, 40% and 43% of the rivaroxaban and warfarin arms, respectively, did not receive VKA or other anticoagulation therapy in the first 30 days after stopping the study drug.⁴³ This may have been partly due to the fact that study participants who discontinue a study early may be more difficult to follow. However, this lack of anticoagulation extended even to patients completing the study, with 7.8% of participants in each arm who completed the study not receiving VKA anticoagulation in the 30 days after the end of the study.⁴⁴

Although the decision to provide anticoagulation therapy should be made on an individual basis after incorporating multiple risk factors, the sponsor did not: 1) pre-specify criteria for transition to appropriate anticoagulation in the 30 days following study-drug discontinuation or 2) provide clear, standardized instructions to investigators on how to transition patients deemed eligible for further anticoagulation. Indeed, the sponsor had no plan in place at all to provide patients (whom it was still following) with the appropriate standard of care and instead left it entirely to the discretion of the study investigators, thus exposing study participants to potential harm (which, it can be argued, may have occurred, based on the excess of strokes in the rivaroxaban arm following discontinuation). We believe this is clearly unethical and represents a failure on the part of the sponsor to ensure that risks to subjects are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, as required by the FDA regulations for the protection of human subjects at 21 C.F.R. 56.111(a)(1).

We therefore call upon the FDA to promptly investigate the adequacy of the institutional review board (IRB) review for all sites participating in the ROCKET trial and to provide a timely response to the following questions:

- Did each IRB make the required determinations under 21 C.F.R. 56.111(a) and provide a reasonable justification for its determinations?
- Were there any IRBs that refused to approve the study? If so, why?
- Were subjects adequately informed about the possible increased risk of stroke due to inadequate anticoagulation during the 30-day follow-up period at the end of the study before informed consent was obtained?

Finally, a critical, related question concerns the fact that many patients were treated suboptimally with warfarin *during* the study period. As noted above, the ROCKET study exposed patients in the warfarin arm to serious risks by failing to maintain therapeutic levels of warfarin (mean TTR 55%) when compared with all previous warfarin-controlled anticoagulant trials (mean TTR 63%-73%). It is particularly concerning that the worst management of warfarin occurred at international trial sites, where oversight is relatively lacking.⁴⁵ Table 2 shows that patients from Eastern Europe comprised the largest number of warfarin-arm participants (38.6%), yet had the lowest TTR (49.7%) of any group. Therefore, we also ask that the FDA provide a timely response to the following questions:

- At what point was the sponsor aware that patients in the warfarin arm, particularly at international study sites (Table 2), were being treated suboptimally compared to patients in previous warfarin-controlled trials?
- What actions did the sponsor take to attempt to address this dangerous situation that may have resulted in excess embolic and/or bleeding events in the warfarin-treated patients during the trial?

Table 2. ROCKET Regional Enrollment and TTR (taken as-is from the FDA backup slides.⁴⁶ This slide shows the alarming disparity in warfarin management during the trial at international vs. North American sites.)

	% of Patients	TTR (%)
Eastern Europe	38.6	49.7
Asia-Pacific	14.8	52.4
Latin America	13.2	55.2
Western Europe	14.8	60.6
North America	18.8	64.1
Total	100	55.2

Conclusion

Given the uncertainty surrounding the efficacy and safety of this drug, and the fact that there are already two existing therapies for the same indication, rivaroxaban should not be approved until appropriate clinical studies are performed ensuring that it is as safe and effective as warfarin used skillfully. Committee members voting in favor of approval clearly had serious reservations relating to the drug's benefit:risk profile, and some went so far as to suggest that it should only be used as third-line therapy. We agree with the opinion of the FDA's clinical reviewers⁴⁷ who urged the agency not to approve rivaroxaban for the prevention of stroke and systemic embolism in patients with atrial fibrillation until these outstanding concerns are addressed. The FDA must also review the design and conduct of the ROCKET trial, including the failure to provide patients with the appropriate standard of care (effective anticoagulation) during the trial and after study-drug discontinuation.

Thank you for taking our comments into account when considering action on NDA #202439 for rivaroxaban.

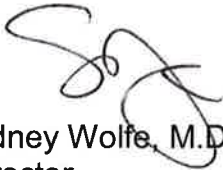
Sincerely,



Sammy Almashat, M.D., M.P.H.
Researcher
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Michael Carome, M.D.
Deputy Director
Public Citizen's Health Research Group



Sidney Wolfe, M.D.
Director
Public Citizen's Health Research Group

Cc: Margaret A. Hamburg, M.D., Commissioner, FDA

¹ Rivaroxaban letter of approval. July 1, 2011. Accessed on September 16, 2011.

http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2011/022406s000ltr.pdf.

² FDA. September 8, 2011: Cardiovascular and Renal Drugs Advisory Committee Meeting Announcement. Accessed on September 16, 2011.

<http://www.fda.gov/AdvisoryCommittees/Calendar/ucm261963.htm>.

³ FDA Draft Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee (CRDAC), Xarelto (rivaroxaban), hereafter referred to simply as "FDA Briefing Document" p.51 and 151. Accessed on September 16, 2011.

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm270795.htm>. The patient population in the ROCKET trial was a high-risk population, when compared to all other phase 2 or 3 warfarin-controlled clinical trials, with 55% of patients having a prior history of stroke, transient ischemic attack, or systemic embolism, compared to 18-29% of patients with such a history in the other trials.

⁴ Fleming TR, Emerson, SS. Evaluating Rivaroxaban for Nonvalvular Atrial Fibrillation — Regulatory Considerations. N Engl J Med. 2011 Oct 5; 10.1056/NEJMp1110639 [online only].

⁵ FDA Briefing Document, p.13.

⁶ FDA Briefing Document, p.14.

⁷ FDA Briefing Document, p.14.

⁸ FDA Briefing Document, p.10.

⁹ FDA Briefing Document, p.16.

¹⁰ FDA Briefing Document, p.57.

¹¹ Pradaxa (dabigatran) drug approval package. Medical Review, p.9-16. Accessed on September 16, 2011. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000TOC.cfm.

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- ¹² Pradaxa (dabigatran) drug approval package. Medical Review, p.46. Accessed on September 16, 2011. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000TOC.cfm.
- ¹³ FDA Briefing Document, p.14.
- ¹⁴ FDA Briefing Document, p.53.
- ¹⁵ FDA Briefing Document, p.54.
- ¹⁶ FDA Briefing Document, p.151.
- ¹⁷ FDA Briefing Document, p.148.
- ¹⁸ FDA Cardiovascular and Renal Drugs Advisory Committee Backup Slides (hereafter referred to simply as "FDA Backup Slides"). NDA 202439 Issues Affecting Interpretation of Efficacy, September 8, 2011. Backup slide 15. Martin Rose, MD, JD, Clinical Reviewer, Division of Cardiovascular and Renal Products. Accessed on October 4, 2011. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM272004.pdf>.
- ¹⁹ FDA Briefing Document, p.162.
- ²⁰ Dolan G, Smith LA, Collins S, Plumb JM. Effect of setting, monitoring intensity and patient experience on anticoagulation control: a systematic review and meta-analysis of the literature. *Curr Med Res Opin.* 2008 May;24(5):1459-72. Epub 2008 Apr 9.
- ²¹ Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. *J Manag Care Pharm.* 2009 Apr;15(3):244-52.
- ²² FDA Briefing Document, p.172, Table 64.
- ²³ FDA Briefing Document, p.173, Table 65.
- ²⁴ D'Angelo A, Della Valle P, Crippa L, Fattorini A, Pattarini E, Viganò D'Angelo S. Relationship between international normalized ratio values, vitamin K-dependent clotting factor levels and in vivo prothrombin activation during the early and steady phases of oral anticoagulant treatment. *Haematologica.* 2002 Oct;87(10):1074-80.
- ²⁵ FDA Briefing Document, p.173, Table 66.
- ²⁶ FDA Briefing Document, p.176, Table 69.
- ²⁷ FDA Briefing Document, p.174.
- ²⁸ FDA Briefing Document, p.62.
- ²⁹ FDA Briefing Document, p.184.
- ³⁰ FDA Briefing Document, p.183.
- ³¹ FDA Briefing Document, p.178-179.
- ³² FDA Briefing Document, p.179.
- ³³ FDA Medical Review for Xarelto (rivaroxaban), p. 180. Accessed on September 20, 2011. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022406Orig1s000MedR.pdf.
- ³⁴ FDA Medical Review for Xarelto (rivaroxaban), p. 180.
- ³⁵ FDA Briefing Document, p.143.
- ³⁶ FDA Briefing Document, p.138, Table 45. 59% of patients were "improved" in the 20mg twice-daily arm compared to 44% of patients in the 40mg once daily arm.
- ³⁷ FDA Briefing Document, p.139.
- ³⁸ FDA Briefing Document, p.143.
- ³⁹ Fleming TR, Emerson, SS. Evaluating Rivaroxaban for Nonvalvular Atrial Fibrillation — Regulatory Considerations. *N Engl J Med.* 2011 Oct 5; 10.1056/NEJMp1110639 [online only].
- ⁴⁰ FDA Briefing Document, p.16.
- ⁴¹ FDA Briefing Document, p.51, 151. The patient population in the ROCKET trial was a high-risk population, when compared to all other Phase 2 or 3 warfarin-controlled clinical trials, with 55% of patients having a prior history of stroke, transient ischemic attack, or systemic embolism, compared to 18-29% of patients with such a history in the other trials.
- ⁴² FDA Briefing Document, p.57.
- ⁴³ FDA Briefing Document, p.175. 47% and 45% of patients in the rivaroxaban and warfarin arms, respectively, who discontinued study treatment prematurely were started on VKA therapy, and 12.8% and 12.1%, respectively, were started on non-VKA anticoagulants in the 30 days following the last dose of blinded study medication, resulting in a total of 59.8% and 57.1% of patients in the rivaroxaban and warfarin arms, respectively being placed on anticoagulation.

⁴⁴ FDA Briefing Document, p.175. Table 69. The number of patients receiving non-VKA anticoagulation was not listed.

⁴⁵ Office of Inspector General. Department of Health and Human Services. Challenges to FDA's ability to monitor and inspect foreign clinical trials. June 2010. Page ii. "FDA inspected 1.9 percent of domestic clinical trial sites and 0.7 percent of foreign clinical trial sites." Accessed on October 4, 2011.

<http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf>.

⁴⁶ FDA Backup Slides, slide 26.

⁴⁷ Although the FDA reviewers recommended against approval, they stated that were rivaroxaban to be approved for this indication on the basis of ROCKET, it should be considered a third-line agent for prevention of stroke in atrial fibrillation patients, with warfarin and dabigatran to be used as initial therapy due to their demonstrated effectiveness for this indication (FDA Briefing Document, p.15).