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APPLICATION NUMBER:
202439Orig1s000

SUMMARY REVIEW

Deputy Division Director Decisional Memo

Date	04 November 2011
From	Stephen M Grant
Subject	Deputy Division Director Decisional Memo
NDA/BLA #	202439
Applicant Name	Janssen Pharmaceuticals
Date of Submission	05 January 2011
PDUFA Goal Date	05 November 2011
Proprietary Name / Established (USAN) Name	XARELTO/ rivaroxaban
Dosage Forms / Strength	Tablet: 20 mg and 15 mg
Proposed Indication	To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
CMC Review	Pei-I Chu
Biopharmaceutics	Tapash K Ghosh
Pharmacology Toxicology Review	Patricia Harlow, Albert DeFelice
Clinical Pharmacology Review	Sreedharan Nair Sabarinath, Tzu-Yun McDowell
Clinical Review	Martin Rose, Preston Dunnmon
Statistical Review	John Lawrence
CDTL Review	Aliza Thompson
Office of Prescription Drug Promotion	Emily Baker, Zarna Patel
Office of Scientific Investigations	Susan Thompson
OSE/DMEPA	Denise V Baugh, Carol A Holquist
OSE/DRISK	Latonia M Ford, LaShawn Griffiths
DHP Clinical Consultant	Ashkan Emadi, Edvardas Kaminskas

OND Office of New Drugs
 CDTL Cross Discipline Team Leader
 OSE Office of Surveillance and Epidemiology
 DMEPA Division of Medication Error Prevention and Analysis
 DRISK Division of Risk Management
 DHP Division of Hematology Products

Action

This memo conveys the Division's decision to approve this application and the basis for that decision. During the review of this application, a separate NDA to market XARELTO (rivaroxaban) for prevention of deep venous thrombosis after hip and knee surgery was approved on July 1 2011 so this NDA's approval will not be as a new molecular entity.

Introduction

Dr. Thompson's CDTL memo ably reviews the background for and important issues presented by this application and can therefore serve as the summary basis of approval. In this memo, I am not going to summarize systematically the medical background or the design and outcomes of the principal clinical trial, ROCKET AF (ROCKET). Rather I intend to review the salient issues germane to the decision to approve because while the CDTL, Dr. Thompson, recommends approval, the primary clinical reviewers of this application, Drs. Rose and Dunnmon, do not. There appears to be no fundamental disagreement among the reviewers of this application about the data generated in ROCKET but rather about the implications of these data. At the dose administered, ROCKET demonstrated robust statistical noninferiority (NI) to warfarin using the agreed upon NI margin of 1.38. This finding was consistent across various analysis populations and various observation periods. Dr. Rose in his section of the primary review concludes, "in no case was the upper limit of the 95% CI more 1.08 for any analysis of the primary endpoint in the overall population." Further, numerically fewer strokes and deaths were observed in XARELTO treated subjects relative to warfarin subjects. The outcomes in the USA and important subgroups were consistent with the overall study results. The principal safety issue for anticoagulants is bleeding; relative to warfarin, the risk of major bleeding in XARELTO subjects in ROCKET was similar but with less intracranial bleeding and more gastrointestinal bleeding. Those results would usually be sufficient for approval to market an anticoagulant in this therapeutic area.

The primary clinical reviewers identify the following reasons in their review of this NDA as the bases for recommending this NDA not be approved:

- The primary basis for recommending that this NDA not be approved relates to the adequacy of international normalized ratio (INR) control among subjects randomized to warfarin in ROCKET. The mean time warfarin subjects in ROCKET spent in the therapeutic INR range (TTR) of 2.0 to 3.0 was 55%, lower than that attained in all other contemporary trials in which warfarin was a comparator (range 62-73%). Both stroke and bleeding outcomes in patients administered warfarin are directly correlated with the TTR. Because there were few subjects whose mean TTR was in the range attained in other contemporary trials (and can be attained in some clinical practices in the USA), ROCKET provides inadequate information to assess the relative safety and efficacy of XARELTO in patients whose warfarin administration can be well-controlled. If XARELTO were inferior to warfarin in patients in whom warfarin administration can be well-controlled then approval could result in American patients having worse outcomes than if not approved. The FDA has a policy enunciated in a 1995 Federal Register (FR) notice signed by William Schultz stating that we will not approve a drug intended to prevent mortality or serious irreversible morbidity if it is inferior to other available therapy. In addition, another anticoagulant drug, PRADAXA (dabigatran), which has been demonstrated superior to warfarin in prevention of stroke in atrial fibrillation patients, is available so there is no unmet medical need for an alternative anticoagulant drug to warfarin.
- In the 30 days after the study ended XARELTO subjects had 22 strokes whereas warfarin subjects had 6 strokes, i.e. XARELTO subjects had nearly four times more strokes.

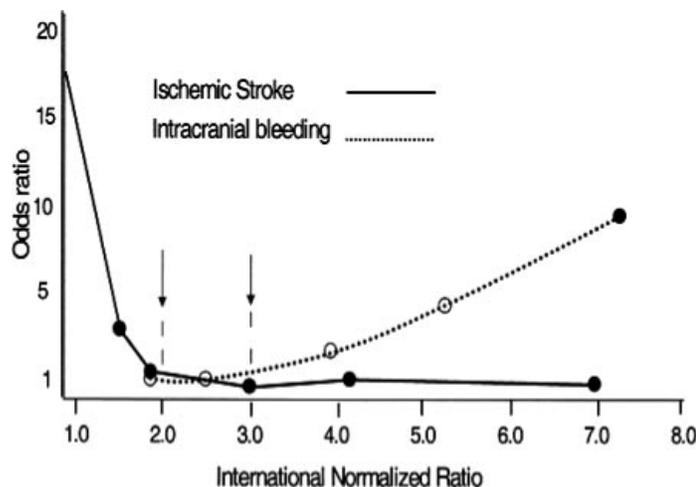
Discontinuation of XARELTO may result in a prothrombotic state. Another clinical study is needed to identify an adequate regimen to prevent strokes when patients are switched from XARELTO to warfarin.

- There was no rational basis for the applicant's choice of the dose tested in ROCKET, 20 mg once a day. The pharmacokinetic/pharmacodynamic properties of rivaroxaban suggest the drug should be administered twice a day.
- If XARELTO is approved for marketing, it should be indicated as second line therapy for those intolerant of warfarin and PRADAXA. It is not clear that XARELTO is as good as warfarin when the INR can be maintained in the therapeutic INR range most of the time. And in the pivotal trial RE-LY, PRADAXA at a dose of 150 mg twice a day was superior to warfarin using an ITT analysis whereas in ROCKET, XARELTO was not superior in a similar analysis.

Most of this memorandum will explain why the Division took a different action than the one recommended by the primary reviewers with a few additional observations at the end.

TTR as a Metric for Assessing Adequacy of Warfarin Control in Clinical Trials

The dose of warfarin must be individualized by adjusting the dose to the INR; too low an INR results in inadequate prevention/treatment of the thrombotic event of interest and too high a dose results in more bleeding than necessary for adequate prevention/treatment of the thrombotic event. The following figure from the 2011 Update of ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation illustrates this relationship when warfarin is being administered for prevention of stroke in patients with atrial fibrillation:



It follows then that the safety/efficacy of warfarin is dependent on how well the INR can be maintained in the therapeutic range of 2.0-3.0. In clinical trials testing a new drug vs. warfarin the relative efficacy/safety will be dependent not only on the properties of the new drug but also on the how well the INR in the warfarin group is controlled. For example, placebo would result in better safety/efficacy relative to a warfarin comparator group whose INR is maintained above 10. Hence to evaluate the results of comparative trials of novel anticoagulants vs. warfarin, it is important to understand how well warfarin was dosed. Time in therapeutic range (TTR) is a measure of the percentage of time the INR of a patient on warfarin is in the therapeutic range of 2.0-3.0 and has been used as a metric for assessing how well the warfarin dose has been controlled in clinical trials. An examination of the figure

above however demonstrates that the clinical consequences of excursions of a similar magnitude above and below the therapeutic range differ. There is a rather steep increase in the probability of ischemic stroke as the INR drops below 2.0 but a more gradual increase in the probability of intracranial bleeding above 3.0.

Comment: A more useful metric than TTR might be a combination of separate measurements of time below therapeutic range and time above therapeutic range weighted according to the clinical consequences of each (i.e., giving more weight to increments in time below the therapeutic range than equivalent increments in time above the therapeutic range).

If an anticoagulant's principal benefit is to reduce ischemic stroke relative to warfarin, TTR is probably useful as a metric of warfarin control because the risk of stroke increases rapidly as the INR drops below 2.0. However if an anticoagulant's principal benefit is to reduce hemorrhagic stroke relative to warfarin, TTR is likely to be less useful as a metric of warfarin control because small increases of the INR above 3.0 do not greatly increase the risk of intracranial bleeding. In the pivotal trial of PRADAXA, RE-LY, there was a relationship between center TTR and efficacy of PRADAXA relative to warfarin; 41 of the 74 fewer endpoint events in the PRADAXA subjects (relative to the warfarin subjects) were ischemic (see PRADAXA USPI). In contrast, 22 of the 31 fewer endpoint events in ROCKET were hemorrhagic stroke and there was not a strong correlation between center TTR and outcomes.

TTR is dependent not only on prescriber skill but also on patient characteristics, such as compliance, concomitant meds, diet, and prior administration of warfarin. For example, no matter how skillful a prescriber may be in adjusting warfarin dose, a noncompliant patient will never achieve a high TTR. Thus there are patients who will never attain a high TTR no matter how skillful the prescriber, and some centers that adjust warfarin will never attain high TTRs because of the characteristics of the patients treated. One of the Advisory Committee members mentioned that the TTR for his entire institution was 54%. Thus it is not, and can not be, clear what value of TTR is necessary to determine that warfarin was administered skillfully. Because results of trials are applicable to patients with characteristics similar to the population enrolled, it is possible to identify a population for whom the results of ROCKET are applicable (and another population to whom the results may not be applicable).

Finally, ROCKET was a "real world" trial in which dosing of warfarin was left to the discretion of the individual investigator. Prior to approval of dabigatran, there were frequent discussions within FDA about the advisability of conducting real world trials vs trials in which warfarin dose was optimized by adjusting it centrally using an algorithm. Some thought real world trials were more likely to provide information about the actual risks and benefits of new therapies when introduced into practice. Others thought new drugs should be demonstrated to be at least similar in outcomes to warfarin when warfarin was optimally managed. We never concluded that either approach was unacceptable (or even that one approach was preferable) so the approach taken by this applicant was acceptable. If the applicant had deliberately attempted to choose investigators that were unfamiliar or unskillful in managing warfarin there would have been an ethical problem because then patients would have received suboptimal care as a result of enrolling in the trial. Although OSI inspections revealed investigators who did not follow US standards for managing warfarin dose, the Division is unaware of any evidence that the applicant deliberately chose investigators because they would not be skillful in managing warfarin dosing.

Application of the 1995 Shultz FR notice

The proper application of the 1995 FR notice signed by William Schultz and a contemporary document signed by then President Clinton and Vice President Gore was much discussed by the review team as well as at the advisory committee. Essentially these documents state the obvious, that it is undesirable to approve for marketing a therapy intended to reduce mortality or serious irreversible morbidity that is worse than available therapy because less effective therapy may displace more effective therapy resulting in worse health outcomes. It should be noted that the policy had to be enunciated because the Food, Drug, and Cosmetic Act only requires drugs be safe and effective to be approved and does not mention comparison to available therapy. The application of the Schultz FR notice to NI studies, the only studies possible when there is existing therapy for conditions resulting in mortality or irreversible serious morbidity, is generally not straight-forward. The Division's interpretation of the Schultz FR notice is that approval should be withheld only if the drug is clearly inferior on an important endpoint to approved therapy in an appropriately conducted trial. For example, the Division has cited the Schultz FR notice to recommend non-approval of a drug for a condition with a high mortality rate in which available therapy substantially reduced mortality while the proposed drug was demonstrated to reduce hospitalization but not mortality in a placebo-controlled trial.

As discussed in the section above TTR appears to have limitations as a metric for assessing warfarin control in ROCKET. The observed mean TTR of 55% in the warfarin subjects in ROCKET is not sufficient to undermine the conclusion that XARELTO is noninferior to warfarin. As used, most analyses found outcomes numerically favored XARELTO and results in the USA where the mean TTR of the warfarin subjects was 63% supported an NI conclusion. In fact, for all patients whose TTR can not be maintained in therapeutic range more than 55-60% of the time, XARELTO is noninferior to warfarin. The final labeling for XARELTO conveys this concept by stating the relative utility of XARELTO in patients whose INR can be well-controlled is unknown.

Excess Strokes after Discontinuation of XARELTO at the End of ROCKET-AF

In ROCKET-AF, study drug was discontinued at the end of the study. Subjects on warfarin generally continued on warfarin while warfarin was generally initiated in XARELTO subjects when or shortly after XARELTO was stopped. When initiating warfarin, doses must be adjusted to attain an INR in the therapeutic range of 2.0 to 3.0, a process that takes some time. As a result, XARELTO subjects took several days longer on average to attain a therapeutic INR compared to warfarin subjects. Put in another way, the XARELTO subjects lacked adequate anti-coagulation for several days longer than warfarin subjects after the study ended. In the 30 days after the study ended XARELTO subjects had 22 strokes whereas the warfarin subjects had 6 strokes (i.e. XARELTO subjects had nearly four times more strokes).

The review team considered two possible explanations for this observation. First, the population enrolled in ROCKET was at high risk for stroke (mean CHADS₂ score of 3.5) so the excess strokes were solely the result of inadequate anti-coagulation. Second, withdrawal of XARELTO results in a prothrombotic state. The Division believes the first explanation is most likely because

1) A relative excess of thrombotic events was not observed during treatment interruptions of more than three days during ROCKET (9 XARELTO subjects had primary endpoint events during 2307 treatment interruptions vs. 8 warfarin subjects during 2668 treatment

interruptions). Intuitively, more strokes would be expected in the XARELTO group because warfarin's pharmacodynamic effects persist for days after administration is stopped whereas rivaroxaban's effect is negligible after a day. Therefore, the observed similarity in outcomes during treatment interruptions is reassuring.

2) A relative excess of thrombotic events other than stroke (such as myocardial infarction), which would have been expected in a prothrombotic state, was not observed after treatment interruption and after study drug discontinuation.

Nonetheless explanation two has not been ruled out. The message that needs to be conveyed to prescribers, however, is the same no matter what the reason for the increase in strokes at study end; i.e., do not discontinue administering XARELTO to a patient until that patient is adequately anti-coagulated by another drug (unless of course there is some compelling reason such as active bleeding) because it will result in excess strokes. Because the increased risk of stroke associated with discontinuing XARELTO can be mitigated by following this advice, it has been placed in a boxed warning consistent with the FDA Guidance published October 2011.

The Division received comments from Public Citizen's Health Research Group indicating concern that the applicant's failure to "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" exposed subjects to unnecessary harm and therefore was unethical. While it is obvious that the applicant can not have intended XARELTO subjects to have had a greater number of strokes while they were being followed because it worsens the apparent risk-benefit profile of XARELTO, it also true that lack of care in designing and conducting ROCKET could have resulted in some XARELTO subjects suffering unnecessary strokes. An examination of the minutes of the independent monitoring data monitoring committee (IDMC) reveals that the leadership of ROCKET was aware of a small excess number of strokes in XARELTO subjects at the end of a similar study in Japan, J-ROCKET. They asked the IDMC "to review unblinded results to aid them in making a recommendation for how to safely transition patients off study drug." The IDMC noted that in many instances subjects in J-ROCKET were not started on warfarin for a period of weeks after discontinuation of study drug. They also reviewed unblinded data of the relative outcomes of subjects who had interrupted or discontinued XARELTO and warfarin in ROCKET and could not identify a major concern. They made a recommendation to the steering committee to encourage investigators to measure an INR after study drug discontinuation to minimize the period of inadequate anticoagulation. These recommendations were followed. Therefore the excess number of strokes in the XARELTO subjects in the 30 days after the study ended does not appear to be the result of unethical behavior by the applicant or any of the applicant's agents.

Switching Patients from XARELTO to Warfarin

The excess in strokes observed in subjects being switched from XARELTO to warfarin at the end of ROCKET generated discussion both by some of the reviewers of this application as well as some members of the Advisory Committee about the need to conduct a clinical study to identify a protocol for safely switching patients from XARELTO to warfarin. The frequency with which patients will switch from XARELTO to warfarin will probably not be high, but some switching is likely to occur. Stopping XARELTO, starting warfarin, and waiting for the INR to reach the therapeutic range was demonstrated in ROCKET to be an unacceptable strategy. The applicant made several suggestions for co-administering XARELTO and warfarin using the INR to guide switching. The Division concluded that these were not acceptable because

in ROCKET, XARELTO was observed to have an effect on INR that varied from subject to subject, and there were no data about the effect of co-administration on the INR. (b) (4)

The Division decided a conservative and reliable approach is to stop XARELTO and then begin a parenteral anticoagulant (like enoxaparin) and warfarin at the same time. The parenteral anticoagulant can be stopped when the INR becomes therapeutic. Co-administering warfarin and a parenteral anticoagulant is a common practice and a protocol for co-administering them is available in the enoxaparin label.

Consideration of Labeling XARELTO as Second Line Therapy

Some on the review team as well as several members of the Advisory Committee suggested that if XARELTO were approved that it be restricted to “second line therapy.” The rationale for this suggestion seems to be as follows:

- It is not clear that outcomes in XARELTO subjects in ROCKET were as good as warfarin subjects whose INR could be well-controlled (see discussion above).
- PRADAXA was shown to be superior to warfarin in RE-LY whereas XARELTO did not demonstrate superiority in ROCKET.
- Therefore XARELTO should be used only in patients whose INRs can not be well-controlled on warfarin and who can not take dabigatran.

This Division did not adopt this suggestion because no specific clinical scenario could be identified that should prompt a health care provider to switch a patient from warfarin or PRADAXA to XARELTO. In fact, some, if not most, of the common problems with warfarin and PRADAXA should not prompt physicians to change therapy. Switching to XARELTO for bleeding may not decrease the bleeding risk; in ROCKET XARELTO patients had a higher rate of gastrointestinal bleeding and bleeding requiring transfusion compared to warfarin. If a patient has a stroke on warfarin or PRADAXA, there is no evidence that switching to XARELTO is better than remaining on warfarin or PRADAXA. If a patient’s INR can not be maintained in the therapeutic INR range because they often do not take warfarin as prescribed, switching to XARELTO may result in a worse outcome because XARELTO has a short half-life and so missing even a single dose results in little anticoagulant activity. After considering the scenarios above, the Division concluded labeling XARELTO as second line therapy might prompt inappropriate switching to XARELTO.

Although the Division chose not to label XARELTO as second line therapy, it did require the label to include in section 1 INDICATIONS AND USAGE a statement that the relative effectiveness of XARELTO and warfarin is unknown when a patient’s INR can be “well-controlled” (the phrase well-controlled as opposed to a specific TTR was adopted because there is no information about how good it has to be controlled, reiterating some of the difficulty with TTR as a metric). As to what was demonstrated in the pivotal trials of PRADAXA and XARELTO respectively, the following information is abstracted from each label:

- PRADAXA at a dose of 150 mg twice a day in RE-LY “significantly reduced the primary composite of stroke and systemic embolism” with a hazard ratio vs. warfarin of 0.65 (95% CI 0.52, 0.81). Its effect on major bleeding was similar to warfarin. The patients in the

warfarin arm were in the therapeutic INR range of 2.0 to 3.0 an average of 64% of the time.

- XARELTO at a dose of 20 mg once a day in ROCKET- AF was demonstrated noninferior but not superior to warfarin for reducing the primary composite of stroke and systemic embolism with a hazard ratio vs. warfarin of 0.88 (95% CI 0.74, 1.03). Its effect on major bleeding was similar to warfarin. The patients in the warfarin arm were in the therapeutic INR range of 2.0 to 3.0 an average of 55% of the time.

Dose of XARELTO administered in ROCKET

Anticoagulants are intrinsically narrow therapeutic range drugs because their principal toxicity, bleeding, is a result of their intended pharmacodynamic activity; too low a dose results in inadequate prevention of pathological thrombosis and consequent serious clinical events and too high a dose results in excessive inhibition of physiologic clotting and excessive bleeding. Therefore, prudent drug development of anticoagulants should include robust investigation of the relationship between dose and outcomes in order to choose reasonable dose(s) for administration to patients.

The Division concurs with all reviewers of this NDA that data adequate to select a dose to be tested in ROCKET were not available when the trial was designed. The applicant chose the dose to be tested in ROCKET based on two small dose-ranging studies. A rather narrow range of doses was explored (20-40 mg qd in one and 10- 30 mg bid and 40 mg qd in the other). The interpretation of the data from these studies was not obvious and the applicant's stated interpretation lacked adequate rationale. When the applicant inquired if the Division concurred with their dose selection, we said that we did not concur. The half-life of rivaroxaban is less than 12 hours (resulting in trough serum concentrations less than 25% of peak concentrations when administered once a day) so we suggested that administering XARELTO twice a day might result in better outcomes. Given the limitations in available information at the time dose(s) to be tested in ROCKET were selected, an additional dose (i.e., in addition to 20 mg once a day) should have been tested.

Nonetheless, the Division allowed ROCKET to proceed. We did so because we lack authority to put trials on clinical hold for inadequate dose selection. We may put a trial on hold if "the protocol for the investigation is clearly deficient in design" [21 CFR 312.42 (b)(2)]. Clearly deficient is a high standard; it was not impossible that the trial testing a 20 mg dose would succeed (as it eventually did, although perhaps not as successfully as it might have had another dose or doses been tested).

Absent significant toxicity, inadequate dose exploration is rarely an impediment to approval. If inadequate dose exploration results in an ineffective dose being tested in a trial, then the trial will fail. And we do not have any data about how different doses might have performed in ROCKET. There was a discussion at the Advisory Committee that the Division might order or encourage the applicant to perform further dose exploration. No study other than an outcomes superiority study is likely to provide evidence of the utility of a different dose. Such a study would have to accumulate a very large number of events to be adequately powered and so would not be available for years. By the time the results were available, it would be likely not to have any utility. Most likely the matter of whether there is a better dose of a factor Xa inhibitor for prevention of stroke in patients with atrial fibrillation will be resolved by other sponsors who are conducting or have conducted other trials of other factor Xa inhibitor s using different doses and/or dosing regimens.

Comment: It should be noted that the Division routinely advises sponsors to test more than one dose in confirmatory trials of antithrombotics and has even suggested novel trial designs that allow testing of two doses without the need to increase sample size. Multiple antithrombotics have failed to be approved or had low utilization after approval because the doses tested were far from optimal and so it is difficult to understand why sponsors have rarely taken this advice.

Finally, as noted above, rivaroxaban absorption is limited above a dose of 10 mg in the fasted state and so doses of 15 mg and greater must be administered with a sizable meal. In clinical studies of the effect of food on XARELTO absorption, the meals consumed were between 600 and 1050 kcal with a rather high fat content. In ROCKET, XARELTO was administered with the evening meal, which typically is the largest meal of the day. In the absence of information indicating the content of a meal necessary to assure absorption similar to that in ROCKET-AF, the label will recommend that XARELTO be taken with the evening meal and the applicant will communicate to prescribers that XARELTO should be taken with the evening meal.

Additional Issues

Desirability of Monitoring for Adjustment of XARELTO Dose

The clinical pharmacology and clinical reviewers demonstrated that there is a linear correlation between rivaroxaban levels and prothrombin time (PT). They also demonstrated that there is also a correlation between PT and risk of bleeding. This applicant has not chosen to utilize this information. In fact, so far as we are aware, none of the other manufacturers/sponsors of other oral anticoagulants that inhibit single coagulation factors have chosen to utilize pharmacokinetic/pharmacodynamic information to explore adjusting dose to optimize safety and efficacy. It is convenient for patients to be able to dispense with the at least monthly monitoring required for warfarin (perhaps increasing the willingness of health care providers to prescribe and patients to take an anticoagulant). However, infrequent monitoring (perhaps at initiation and yearly thereafter) to assure appropriate dosing of drugs that prevent stroke and cause bleeding may improve outcomes and be acceptable to patients.

Treatment Strategies for XARELTO-Induced Bleeding

The label for COUMADIN provides specific recommendations for treatment of hemorrhage. No such recommendations can be provided for XARELTO. And the label states that XARELTO increases the risk of bleeding requiring transfusion relative to warfarin. Therefore, it is unlikely that XARELTO will be an appropriate choice for patients at high risk of bleeding. Dr. Thompson recommends a PMR to explore treatment strategies for bleeding occasioned by XARELTO and for enhanced pharmacovigilance. The Division decided not to require a PMR. The applicant already has adequate incentive to develop an antidote or therapy to treat bleeding occasioned by XARELTO because either would make the drug more attractive to health care prescribers, resulting in increased utilization. The value of increased pharmacovigilance is uncertain; XARELTO causes bleeding and interpretability of observational data related to bleeding is limited because efficacy can not be readily captured.

Analysis of Future Trials of Anticoagulants for Preventing Stroke in Atrial Fibrillation

During the last few years several novel anticoagulants have been under development; two have now been approved, with more likely to come. It strikes this reviewer that evaluating these drugs by balancing the effect on "stroke" reduction vs "bleeding" is a bit too simple. Strokes are comprised of ischemic strokes and intracranial hemorrhage and these should be

analyzed separately. As mentioned above, in RE-LY PRADAXA reduced the risk of ischemic stroke more than hemorrhagic stroke relative to warfarin whereas almost the entire effect of XARELTO relative to warfarin was due to reduction of hemorrhagic stroke. Whether these differing outcomes are the result of pharmacology, dose, chance (or perhaps something else) is not clear. Similarly, the clinical consequences of bleeding into the gastrointestinal tract are quite different from bleeding into the head and so should be analyzed separately. In ROCKET, stating the risk of “major” bleeding was about the same for warfarin and XARELTO obscures the fact that the relative effects on gastrointestinal bleeding and intracranial hemorrhage were quite different, similar to results observed in RE-LY with dabigatran. The reasons for the differential effect are not intuitive. It may be that some action of warfarin predisposes to intracranial bleeding.

Acknowledgements

The Division’s conclusions rest entirely upon the excellent review performed by this review team. The decision was made difficult by the limitations in the design and conduct of ROCKET AF. Although ultimately coming to a different conclusion than some of the reviewers, both the Division Director and the Deputy shared the team’s concerns about this NDA.

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/s/

STEPHEN M GRANT
11/04/2011