# It Is Time to Ask Patients What Outcomes Are Important to Them

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**ABSTRACT**

**OBJECTIVES:** To identify the outcomes de-sited by patients (and their family members) with abdominal or back pain and to compare patient and physician opinions regarding the importance of each outcome.

**STUDY DESIGN:** Mixed methods.

**METHODS:** After identifying 21 potentially important outcomes from the literature and telephone interviews with patients and family members, we asked 40 patients, 11 family members, and 11 primary care physicians in telephone interviews to rate the importance of each outcome to patients on a scale of 1 to 5 scale (5 = most important), stratified by pain location.

**RESULTS:** Mean patient ratings of the 21 outcomes ranged from 3.3 to 5, with the average rating across all items higher for patients with back pain than those with abdominal pain (4.50 vs 4.09; $P = .049$). Physicians rated the importance of these outcomes to patients significantly lower than the patients did for both abdominal pain (4.1 vs 3.5; $P = .04$) and back pain (4.5 vs 3.6; $P = .0003$). Family member ratings were similar to those of the patients (4.3 vs 4.2; $P = .8$), whereas physicians rated the importance to patients to be an average of 0.6 points lower than the ratings of patients for abdominal pain and 0.8 points lower for back pain.

**CONCLUSION:** Many outcomes are important to patients and their family members, but they mostly represent quality-of-life events rather than the symptom and function measures heretofore focused on by researchers. Physicians appear to rate most of these outcomes somewhat lower in importance.

Patient outcomes and their measurement for comparative effectiveness research, performance measurement, and patient care are increasingly important. Early measures of patient outcomes were usually selected from the perspective of a clinician, but there was a shift to a more patient-centric perspective 15 years ago as measures of health status and quality of life.[1] By 2010, patient outcomes had attained such priority nationwide that the Patient-Centered Outcomes Research Institute (PCORI) was established to emphasize incorporating patient viewpoints and outcomes in every aspect of healthcare research.[2]

This large shift has required the development of patient-reported outcomes measures (PROMs). Subsequently, the National Institutes of Health established the Patient-Reported Outcomes Measurement Information System (PROMIS) in 2004 with the goal of "providing clinicians and researchers access to efficient, precise, valid, and responsive…measures of health and well-being."[3] Although this system was primarily created for clinical research, it is rapidly becoming the standard source of PROMs for all purposes. The PROMIS Assessment Center currently contains measure sets that are publicly available in 19 domains for assessing the physical, mental, and social health of both adults and children.

However, the PROMIS tools largely measure specific patient functions and symptoms and seem to assume that such specific measures are the only outcomes that matter to patients and their families. The PROMIS website does not describe any involvement of patients in the selection of its outcome measures, and no publications describe attempts to learn from patients what outcomes they care most about. Although patients probably do care about relief from symptoms and improvement in function, there may also be other outcomes that are equal or more important to them.

Therefore, we developed this study to discover what outcomes patients and their family members cared about among those who had experienced back or abdominal pain problems that were serious enough to require advanced diagnostic imaging studies. We focused on patients with actual experiences, thinking they should be most aware of outcomes important to them. After identifying potentially important outcomes through preliminary open-ended interviews, we surveyed patients, their family members, and primary care physicians to learn their rating of the importance of each outcome and then compared these ratings among patients, family members, and physicians.

## METHODS

### Setting

We conducted this study among the patients receiving care from an 800-physician multi-specialty medical group in the Minneapolis-St. Paul metropolitan area. In order to facilitate access to health plan claims data for these patients for a later phase of the study, patient recruitment was limited to the 60% with insurance from the affiliated health plan; this population includes patients on prepaid medical assistance and a racial and ethnic profile similar to that of the Twin Cities metropolitan area.

### Pilot Interviews

In order to create a list of potentially important patient outcomes, we randomly identified adults who had undergone either a magnetic resonance imaging (MRI) or computed tomography (CT) scan for abdominal or back pain about 1 year prior. We first sent these individuals a letter explaining the study and providing an opportunity to opt out of further recruitment contacts. If they did not opt out, trained interviewers called them to assess their willingness to participate in a telephone interview, during which they were asked about all of the outcomes they had wanted from the care of their pain problem. Interviewers next read them a list of other possible outcomes that had been generated by the research team (which included a patient co-investigator) and asked them to rate the importance of each outcome on a scale of 1 to 5 (5 = extremely important, 1 = not at all important). Finally, they were asked again about any other outcomes they might have thought of. We gave completed interviewees a $40 gift card—this incentive was mentioned in both the pre-notification letter and introductory script. Out of 7 patients contacted within 3 telephone attempts, 6 agreed to participate and completed the interview. Two of those 6 said there was a family member who was very familiar with their pain problem and would be willing to be contacted, so we also recruited them and completed interviews. The responses from these 8 people were so consistent that no further pilot interviews seemed needed.

### Patient/Family Interviews

Following the pilot, in hopes of completing 40 patient telephone interviews, we identified an additional random pool of 83 adult patients who had experienced a first CT or MRI scan of the back or abdomen for pain about 1 year prior. We followed the same protocol used in the pilot; the interview script—revised after the pilot calls—confirmed eligibility, obtained demographic information, and asked about the most important outcomes desired from the medical care of their problem. Then we asked subjects to rate a revised list of 21 outcomes (see **Table 1** for the list in the order in which items were asked) on an importance scale of 1 to 5 (again, 5 = extremely important, 1 = not at all important). Finally, we asked them whether there was a family member who was familiar with their problem who might be willing to complete a similar interview. If so, we made contact arrangements and the family member interview followed the same process. Interviews lasted an average of 15 minutes and all respondents were sent a $40 gift card.

### Physician Interviews

We identified and recruited practicing adult primary care physicians through the help of a co-investigator (CV) at the Institute for Clinical Systems Improvement for interviews by our practicing primary care physician co-investigator (JB). Because the physicians had not had a specific personal experience to reference, we provided them with common case scenarios for patients with back or abdominal pain as context for their answers. We asked what outcomes they thought would be most important to the

**Table 1. Patient Outcomes (in the order read to interviewees)**

1. To find out the cause of the pain.
2. To understand what may happen to you because of the problem.
3. To get rapid and complete relief from pain and other symptoms.
4. To prevent this problem from occurring again.
5. To experience no complications or side effects.
6. To be assured that no unexpected, unrelated problems develop during this time.
7. To trust that the treatment plan is appropriate.
8. To minimize discomfort from the tests used to assess the pain.
9. To minimize or avoid the need for further tests and medical visits.
10. To minimize radiation exposure in the course of my care.
11. To minimize or avoid use of medication.
12. To avoid being hospitalized.
13. To avoid surgery.
14. To prevent long-term loss of function.
15. To return to normal life functions.
16. To return to work and productivity as soon as possible.
17. To return to leisure/sports activities as soon as possible.
18. To avoid placing a burden or stress on family members.
19. To avoid personal costs for care.
20. To be satisfied with the way care was delivered.
21. To be satisfied with the results of the care.

scenario patients; then they were asked to rate each of the 21 outcomes (see Table 1) identified from patients on the same 1-to-5 scale from the perspective of their patients. They were also asked about the most important outcomes from their perspective as a clinician.

### Analysis

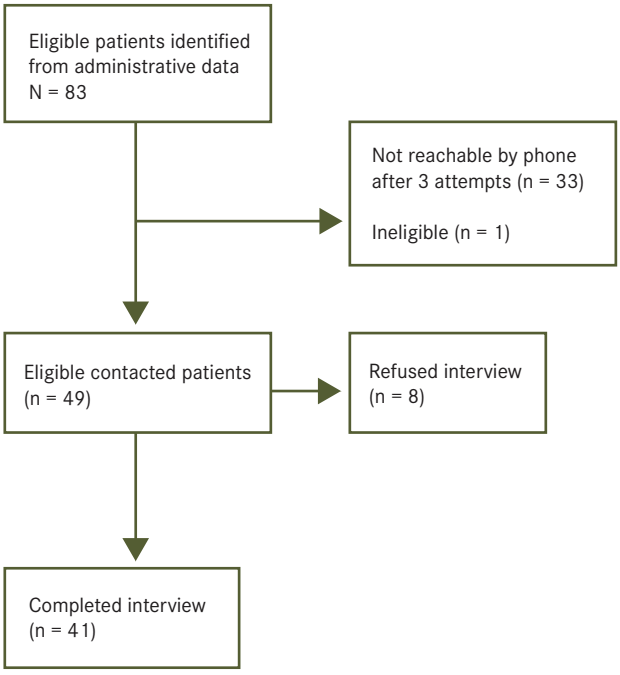
Associations between type of pain and patient attributes were tested using contingency tables and Pearson's $\chi^2$ and Fisher's exact tests. Independent samples *t* tests were used to test differences in outcome importance ratings between abdominal and back pain patients, as well as differences in outcome importance ratings between patients and physicians. The study has 80% power ($\alpha = 0.05$, 2-sided test) to detect a difference of 0.9 standard deviations (SDs) in the mean outcome rating from abdominal and back pain patients. An $\alpha$ of 0.05 was considered statistically significant, 2-tailed tests were used, and there was no correction for multiple testing. Analyses were conducted using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

**Table 2. Characteristics of Patients Interviewed**

| CHARACTERISTIC | ABDOMINAL PAIN | BACK PAIN | TOTAL |
|---|---|---|---|
| **N** | **21** | **19** | **40** |
| Female | 20 (95%) | 17 (89%) | 37 (92%) |
| White | 20 (95%) | 15 (79%) | 35 (88%) |
| Age, years | | | |
| <41 | 4 (19%) | 2 (10%) | 6 (15%) |
| 41-60 | 10 (48%) | 14 (74%) | 24 (60%) |
| >60 | 7 (33%) | 3 (16%) | 10 (25%) |
| Medicare | 5 (24%) | 3 (16%) | 8 (20%) |
| Medicaid | 0 (0%) | 3 (16%) | 3 (8%) |
| Married | 13 (65%) | 12 (63%) | 25 (64%) |
| Education | | | |
| High school or less | 2 (10%) | 5 (26%) | 7 (18%) |
| Some college | 5 (25%) | 6 (32%) | 11 (28%) |
| College grad | 13 (65%) | 8 (42%) | 21 (54%) |
| Employment | | | |
| Employed | 12 (57%) | 13 (68%) | 25 (62%) |
| Retired | 6 (29%) | 3 (16%) | 9 (22%) |
| Other | 3 (14%) | 3 (16%) | 6 (15%) |
| First time with this pain | 12 (57%) | 7 (37%) | 19 (48%) |
| First scan for this problem | 20 (95%) | 14 (74%) | 34 (85%) |
| Type of scan[a] | | | |
| CT | 21 (100%) | 0 | 21 (52%) |
| MRI | 0 | 19 (100%) | 19 (48%) |

[a] $P < .001$, Fisher's exact test.

**Figure 1. Patient Participation Flow Diagram**




## RESULTS

Of 83 patients with call attempts, we could not reach 33, and 1 of those contacted was ineligible as they reported not having the scan (see **Figure 1**). Of the 49 eligible patients who could be contacted, 41 completed interviews—but the data from 1 was inadvertently lost—for a participation rate of 84% of eligible patients contacted, or 49% of all those attempted. Twelve patients nominated a family member who had been actively involved in the care of their pain problem for interviews, and 11 of those 12 completed them. Responding patients were similar to nonresponders by age, race, Medicare insurance, pain type, and scan type. The major difference was that responders were much more likely to be females (92.5% vs 46.2%; $P < .001$) and to be on Medicaid (7.5% vs 0%; $P = .045$).

The characteristics of participants are listed by pain type in **Table 2**. The majority were female and white. Aside from the type of scan, none of the other characteristics differed significantly by pain type. Ten of the family members were spouses and 1 was a daughter. Family member characteristics were similar to those of the patients except that family members were more likely to be male (7 of 11 [63%]) and married (10 of 11 [91%]) than patients as a whole.

Seventeen primary care physicians were identified as potential

**Table 3. Patient Importance Ratings for Outcomes**

| | TOTAL | | ABDOMINAL PAIN | | BACK PAIN | | |
|---|---|---|---|---|---|---|---|
| **N** | **40** | | **21** | | **19** | | |
| **Outcome** | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | **Diff** |
| 1. Find out the cause of the pain | 4.9 | 0.4 | 5.0 | 0 | 4.7 | 0.6 | 0.3 |
| 2. Trust treatment plan is appropriate | 4.7 | 0.6 | 4.6 | 0.7 | 4.8 | 0.4 | -0.2 |
| 3. Return to normal life functions | 4.7 | 0.6 | 4.6 | 0.6 | 4.7 | 0.6 | -0.1 |
| 4. Satisfied with results of care | 4.7 | 0.8 | 4.6 | 0.9 | 4.8 | 0.5 | -0.2 |
| 5. Understand what may happen | 4.6 | 0.7 | 4.5 | 0.9 | 4.8 | 0.4 | -0.3 |
| 6. Prevent recurrence | 4.6 | 0.9 | 4.4 | 1.1 | 4.8 | 0.5 | -0.4 |
| 7. Prevent long-term function loss | 4.6 | 0.9 | 4.5 | 1.1 | 4.7 | 0.6 | -0.3 |
| 8. Return to work/productivity ASAP | 4.5 | 0.9 | 4.3 | 1.0 | 4.7 | 0.6 | -0.4 |
| 9. Satisfied with how care delivered | 4.5 | 0.9 | 4.4 | 1.0 | 4.7 | 0.6 | -0.3 |
| 10. No complications or side effects | 4.3 | 1.0 | 4.2 | 1.1 | 4.4 | 0.8 | -0.2 |
| 11. No unrelated problems develop | 4.2 | 1.2 | 4.2 | 1.2 | 4.2 | 1.2 | 0.0 |
| 12. Get rapid & complete relief | 4.2 | 1.0 | 4.4 | 1.1 | 4.1 | 0.9 | 0.3 |
| 13. Avoid hospitalization | 4.1 | 1.2 | 3.7 | 1.4 | 4.5 | 0.8 | -0.8[a] |
| 14. Avoid surgery | 4.1 | 1.3 | 3.7 | 1.4 | 4.6 | 1.0 | -0.9[a] |
| 15. Avoid burden/stress on family | 4.1 | 1.1 | 3.7 | 1.2 | 4.5 | 0.7 | -0.8[a] |
| 16. Minimize tests & medical visits | 3.9 | 1.1 | 3.7 | 1.1 | 4.1 | 1.0 | -0.4 |
| 17. Minimize radiation exposure | 3.9 | 1.4 | 3.6 | 1.5 | 4.3 | 1.2 | -0.7 |
| 18. Avoid personal costs of care | 3.9 | 1.4 | 3.4 | 1.7 | 4.5 | 0.8 | -1.0[a] |
| 19. Minimize medications | 3.8 | 1.1 | 3.5 | 1.2 | 4.3 | 0.6 | -0.8[a] |
| 20. Return to leisure activities ASAP | 3.8 | 1.1 | 3.5 | 1.2 | 4.2 | 1.0 | -0.7 |
| 21. Minimize test discomfort | 3.7 | 1.3 | 3.3 | 1.3 | 4.1 | 1.1 | -0.8[a] |

ASAP indicates as soon as possible; Diff, difference.

[a] $P < .05$

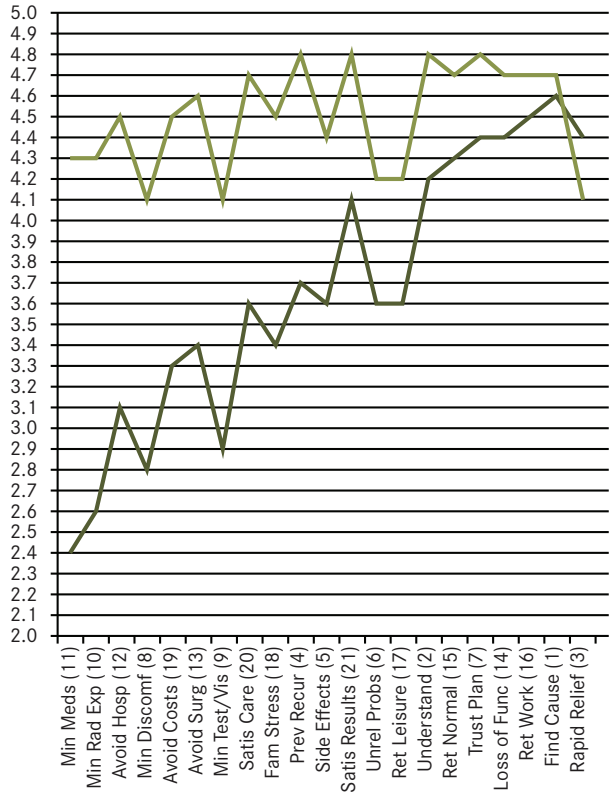
participants in the second-stage interview, but 4 of them referred us to colleagues who agreed to participate and completed interviews along with 7 others. Each physician was from a different clinic: 4 were from the Twin Cities metro area and 7 were from the rest of the state; 2 were internists and 9 were family physicians; 3 were female and 8 male; and 6 had been in practice for 26 to 43 years, 2 for 12 to 15 years, and 3 for 4 to 6 years.

In the initial open-ended phase of the pilot patient interviews, the main outcome identified by most patients and family members was to learn the cause of the pain. Seven of the other outcomes on the list were also mentioned spontaneously before respondents were given the list to rate. Only 1 ("minimize discomfort from the tests used to assess the pain") was raised that was not on the list.

**Table 3** contains the mean importance ratings by patients for the 21 outcomes and the difference between those ratings by patients with abdominal pain versus those with back pain. There was considerable overlap between the 2 groups, although patients with abdominal pain gave lower importance ratings for nearly all outcomes than did patients with back pain; the overall mean rating was 0.4 points lower than those with back pain (4.09 vs 4.50; $P = .049$). Higher ratings were given by patients with abdominal pain for only 2 outcomes: to find the cause and to get rapid and complete relief. The overall mean rating of the 21 outcomes from family and patients was similar (4.32 for family, 4.28 for patients; $P = .86$). Most (8 of 11) family members were connected with patients who had experienced abdominal pain. Importance ratings by family members of abdominal patient were the same or directionally higher than those of abdominal pain patients for 16 of 21 outcomes, and there were no statistically significant differences.

**Figures 2** and **3** provide graphic comparisons between patient and physician importance ratings for each of the outcomes, ordered by the magnitude of the difference between them. For abdominal pain, physicians rated the importance to patients to be an average of 0.6 points lower than the ratings of patients (3.53 vs 4.09; $P = .04$); for back pain, that difference was 0.85 points lower (3.65 vs 4.50; $P = .0003$). Each of the 4 individual outcomes with statistically significantly lower physician ratings for abdominal pain was also significantly lower for back pain. There

**Figure 2. Patient and Doctor Importance Ratings for Back Pain, Ordered by Rating Differences**




Discomf indicates discomfort; exp, exposure; fam, family; func, functioning; hosp, hospital; min, minimize; meds, medications; prev, prevent; pts, patients; probs, problems; rad, radiation; ret, return; recur, recurrence; satis, satisfactory; surg, surgery; unrel, related; vis, visits.

Numbered as in Table 1.

were also another 9 of the outcomes for back pain with statistically significant physician-patient differences. Moreover, all of the items with $P < .01$ or less were in the back pain list. The outcomes with greatest agreement between patients and physicians were finding the cause, getting rapid and complete relief, and returning to work and productivity as soon as possible. For most outcomes, the 3 younger physicians provided lower ratings than the 8 with longer practice experience. Patient ratings of abdominal pain outcomes tended to show more variability than physician ratings, with 15 of the 21 SDs for abdominal pain outcomes being higher for patients than physicians. However, for back pain, the pattern was reversed, with 7 of the 21 SDs for back pain outcomes being higher for patients than physicians.

When the physicians were asked about the most important outcomes from their perspective, 5 highlighted making a diagnosis, 6 thought it was needed to guide treatment, and 4 wanted to rule out something serious. Four physicians also noted a reduction in symptoms and 3 identified restoration of normal function as soon as possible. Single physicians mentioned humane care, prognosis, and good access to care.

## DISCUSSION

These patients and their families rated a wide variety of outcomes from their care as important. Although there were differences between the average importance ratings by type of pain, the differences were mostly small and all of the outcomes we asked about had relatively high ratings that were similar between patients and family members. Finally, the primary care physician interviewees tended to rate each of these outcomes as having lower importance than did patients or their families, even though the physicians were asked to rate the importance of each outcome from the patients' perspective rather than from their own. The similar shape of the importance difference curves in Figures 2 and 3 across all of these outcomes suggests that these differences are real. Such differences highlight the importance of asking patients—both individually and collectively—about what outcomes are important to them.

The results of this study raise important questions about what approach should be used to identify PROMs. The current focus on using measures that have been identified by researchers and those limited to specific functions and symptoms will likely not capture the same outcomes that patients themselves might identify as important. McClimans, in his study, has objected to the whole idea of standardized questions, instead proposing a theoretical framework for thinking about PROMs that understands them "as posing genuine questions to patients—questions that are open to reinterpretation [and context]."[4] He particularly objects to measures that break down the outcome into a series of sub-questions and that assume their sum fully captures the overall outcome. McKenna raises a similar concern in his study, while emphasizing the importance of a hard science approach to measure development.[5]

Only 1 of the outcomes that these patients thought were important (ie, to get rapid and complete relief from pain and other symptoms) would be partially measurable by the PROMIS measurement sets established by the National Institutes of Health to measure patient outcomes.[6] PROMIS has developed questionnaires to ask about pain, fatigue, gastrointestinal symptoms, arm and leg function, sexual function, sleep, physical activity, affect, cognition, self-efficacy, substance use, social support, peer and family relationships, and social roles and activities. There are also global health status questions.[7,8] The individual question sets (short forms) for each of these domains varies from 4 to 10 questions selected from banked sets that contain as many as 121 questions. Their psychometric qualities are mostly well studied, and they are a wonderful resource for researchers, but there has been no patient involvement in selecting or reviewing these measures.[3,7,8]

The other main source for patient outcome measures is the National Quality Forum. It has endorsed nearly 700 measures created by other organizations, 208 of which are identified as outcome measures.[9] Although most of the latter are clinical outcomes related to specific conditions, some do address patient function, usually in relation to a specific procedure—few are as

generic as the outcomes considered important by our patient subjects. A similar resource in Britain, the Health and Social Care Information Centre, began work in 2009 on PROMs and currently has measurement sets in place for hip and knee replacement, hernia repair, and varicose vein treatment—again, mostly clinical and specific for a procedure and condition.[10] There is no indication on its website that patients had any role in identifying these measures.

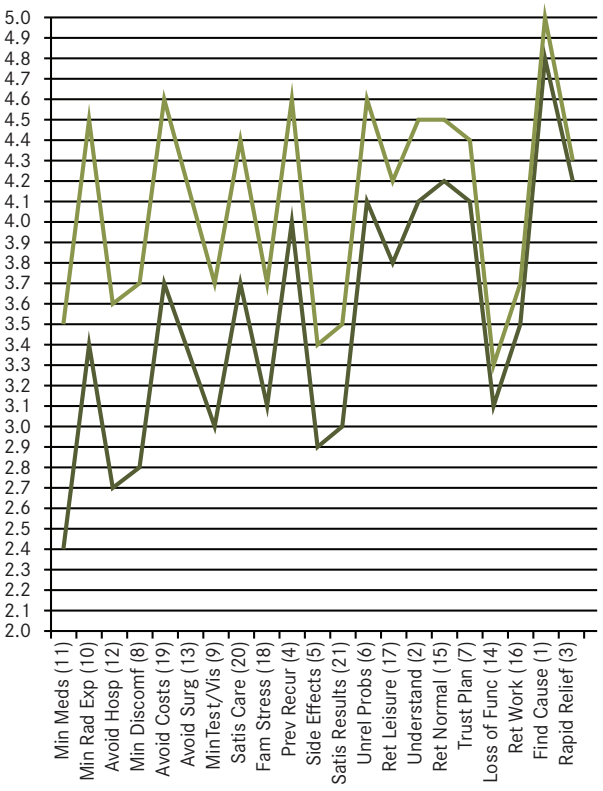
PCORI has prioritized developing patient-centered outcome measures and is becoming a resource for PROMs. It is developing standards for such measures, but so far has not created or endorsed any specific measures. Its Methodology Committee has recommended that patients be included in the peer review process for grant proposals, and it has a standard requiring that researchers "engage people representing the population of interest and other relevant stakeholders in ways that are appropriate and necessary in a given research context."[11]

Developing outcome measures that are meaningful to patients is a new endeavor for healthcare, and accordingly, it will take some time to get it right. Once we know what patients want measured, learning where to most efficiently and accurately obtain that information is another challenge. Although it might seem obvious that the best source of data is directly from patients, this may not always be feasible because of the cost and difficulty tracking and obtaining responses. Thus, we need to learn whether some of those outcomes can be obtained from medical records or insurance claims data. Yet another challenge will be learning how to incorporate those measures into the daily practice of medicine. Black suggests in his study that outcome measures could be transformative for healthcare, but admits that their use in routine practice is still uncommon, and identifies a series of challenges.[12] As if to demonstrate that, his group recently published a study using PROMs to compare surgeons and concluded that the choice of outcome measure can substantially alter a surgeon's rating.[13] Valderas et al performed a systematic review of the literature on the impact of measuring PROMs in clinical practice.[14] They confirmed that "contexts and interventions that will yield important benefits remain to be clearly defined."

## Limitations

Our findings in this study are limited to patients with 2 types of clinical situations: back pain that tends to be chronic or recurrent and abdominal pain that tends to be acute. The underlying disease processes and patient impacts of these 2 situations are both heterogeneous and different, which highlights how important it is to survey patients across a broad range of contexts if the goal is to fully understand patient preferences. The advantage of surveying patients as we did was that having their own recent experience with these potentially serious and disabling problems should have made their responses less abstract. All of the sample sizes in this study were small, and the subjects were not especially diverse or representative nationally, so these findings require confirmation in larger more representative, diverse samples. It is also likely that we have not identified all of the important outcomes.

**Figure 3. Patient and Doctor Importance Ratings for Abdominal Pain, Ordered by Rating Differences**

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Numbered as in Table 1.

Nevertheless, the findings are especially important in suggesting that there are a wide variety of outcomes that are important to patients and their families, outcomes that are not necessarily limited to relief of particular symptoms or recovery of certain functions. Thus far, most of the attention to PROMs has focused on the psychometric and feasibility aspects of measures that are limited to specific symptoms and functions. It might be wise to first obtain more input from patients before once again learning that the outcomes we measure so well have little relevance to what patients want to know before they make decisions about their care.

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# Published safety outcomes in real-world patients, from observational studies

*Based on the following registries, claims databases, and studies: Optum Labs=16,253; IMS Health LifeLink=1,649; Truven Health=5,563; Danish registry=1,303; XAMOS=8,778; Symphony=3,654; ORTHO-TEP=1,043; Japanese registry=1,035; Dresden NOAC=1,776; DOD database=27,467; XANTUS=6,784.


## BEYOND EXTENSIVE RANDOMIZED CLINICAL TRIALS, PUBLISHED SAFETY OUTCOMES FROM OBSERVATIONAL STUDIES OF REAL-WORLD PATIENTS*[1-11]

*Based on the following registries, claims databases, and studies: Optum Labs=16,253; IMS Health LifeLink=1,649; Truven Health=5,563; Danish registry=1,303; XAMOS=8,778; Symphony=3,654; ORTHO-TEP=1,043; Japanese registry=1,035; Dresden=1,776; DOD database=27,467; XANTUS=6,784.

## IMPORTANT SAFETY INFORMATION

**WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO® INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA**

**A. PREMATURE DISCONTINUATION OF XARELTO® INCREASES THE RISK OF THROMBOTIC EVENTS**

**Premature discontinuation of any oral anticoagulant, including XARELTO®, increases the risk of thrombotic events. If anticoagulation with XARELTO® is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.**

**B. SPINAL/EPIDURAL HEMATOMA**

**Epidural or spinal hematomas have occurred in patients treated with XARELTO® who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:**

- **Use of indwelling epidural catheters**
- **Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants, *see* Drug Interactions**
- **A history of traumatic or repeated epidural or spinal punctures**
- **A history of spinal deformity or spinal surgery**
- **Optimal timing between the administration of XARELTO® and neuraxial procedures is not known**

**Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.**

**Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.**

**CONTRAINDICATIONS**

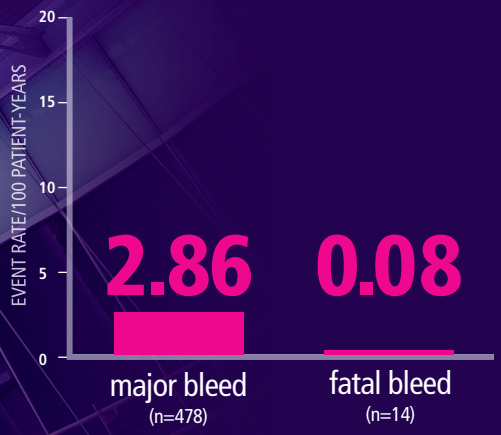
- Active pathological bleeding
- Severe hypersensitivity reaction to XARELTO® (eg, anaphylactic reactions)

**Please see Important Safety Information throughout.**
**Please see accompanying Brief Summary of full Prescribing Information, including Boxed WARNINGS, or visit www.XareltoHCP.com/PI.**

# Real-world safety outcomes from one ongoing US study of 27,467 nonvalvular AF patients[11]

Results based on 15 months of data from an ongoing, 5-year postmarketing safety surveillance study to evaluate major bleeding in patients receiving XARELTO® in a real-world clinical setting. Cases of major bleeding were identified through electronic health records from the US Department of Defense database, from January 1, 2013, to March 31, 2014.

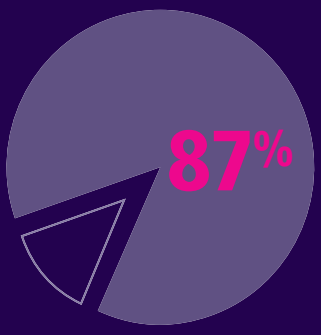
## RATES OF BLEEDING




**0.1%** ICH (n=36)

**1.5%** GI bleed (n=423)

## COMORBID PATIENTS STUDIED




with comorbidities including:

diabetes
heart failure
renal disease

Mean age: 76

RESULTS ARE NOT INTENDED FOR DIRECT COMPARISON WITH CLINICAL TRIALS

A validated computer database algorithm developed by Cunningham et al, which identifies bleeding-related hospitalizations from a primary discharge diagnosis, was used to identify major bleeding events in this study. The definition of major bleeding is not an exact match with the ROCKET AF trial.

**LIMITATIONS:** This is a retrospective study and there is no comparator arm in the trial. Differences in study design, patient populations, definition of safety outcomes, and data collection methods make it difficult to make comparisons with clinical trials.[11]

## RATES OF BLEEDING IN ROCKET AF (N=7,111)[12†]:

- The event rate per 100 patient-years was 3.6 (n=395) for major bleed and 0.20 (n=27) for fatal bleed[‡]
  - 0.8% of patients experienced an ICH (n=55) and 3.1% of patients experienced a GI bleed (n=221)

AF = atrial fibrillation; GI = gastrointestinal; ICH = intracranial hemorrhage.

†XARELTO® was evaluated versus dose-adjusted warfarin in more than 14,000 patients with nonvalvular AF at moderate to high risk for stroke in a rigorously designed, multicenter, randomized, double-blind, double-dummy, event-driven phase III trial. XARELTO® demonstrated effective reduction in the risk of stroke and non-CNS systemic embolism in patients with prior stroke or multiple comorbidities.[12]

‡Major bleeding from ROCKET AF study was defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥2 g/dL, transfusion of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome.[12]

## SIX INDICATIONS STRONG

- To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). There are limited data on the relative effectiveness of XARELTO® and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled
- For the treatment of deep vein thrombosis (DVT)
- For the treatment of pulmonary embolism (PE)
- For the reduction in the risk of recurrence of DVT and of PE following initial 6 months treatment for DVT and/or PE
- For the prophylaxis of DVT, which may lead to PE in patients undergoing knee replacement surgery
- For the prophylaxis of DVT, which may lead to PE in patients undergoing hip replacement surgery

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rivaroxaban tablets




## IMPORTANT SAFETY INFORMATION (cont'd)

### WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events After Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including XARELTO®, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO® to warfarin in clinical trials in atrial fibrillation patients. If XARELTO® is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Risk of Bleeding:** XARELTO® increases the risk of bleeding and can cause serious or fatal bleeding. Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue XARELTO® in patients with active pathological hemorrhage.
  - A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable.
  - Concomitant use of other drugs that impair hemostasis increases the risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, and NSAIDs.
- **Spinal/Epidural Anesthesia or Puncture:** When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis. To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. An epidural catheter should not be removed earlier than 18 hours after the last administration of XARELTO®. The next XARELTO® dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of XARELTO® is to be delayed for 24 hours. Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently to detect any signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), or bowel and/or bladder dysfunction. Instruct patients to immediately report if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.
- **Use in Patients With Renal Impairment:**
  - **Nonvalvular Atrial Fibrillation:** Avoid the use of XARELTO® in patients with creatinine clearance (CrCl) <15 mL/min since drug exposure is increased. Discontinue XARELTO® in patients who develop acute renal failure while on XARELTO®.
  - **Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE:** Avoid the use of XARELTO® in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population.
  - **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:** Avoid the use of XARELTO® in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on XARELTO® should discontinue the treatment.
- **Use in Patients With Hepatic Impairment:** No clinical data are available for patients with severe hepatic impairment. Avoid use of XARELTO® in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy, since drug exposure and bleeding risk may be increased.
- **Use With P-gp and Strong CYP3A4 Inhibitors or Inducers:** Avoid concomitant use of XARELTO® with combined P-gp and strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, and conivaptan). Avoid concomitant use of XARELTO® with drugs that are P-gp and strong CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin, St. John's wort).
- **Risk of Pregnancy-Related Hemorrhage:** In pregnant women, XARELTO® should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO® dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO® cannot be monitored with standard laboratory testing and is not readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (eg, a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).
- **Patients With Prosthetic Heart Valves:** The safety and efficacy of XARELTO® have not been studied in patients with prosthetic heart valves. Therefore, use of XARELTO® is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients/Patients Who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of XARELTO® is not recommended acutely as an alternative to unfractionated heparin in patients with pulmonary embolism who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

### DRUG INTERACTIONS

- Avoid concomitant use of XARELTO® with other anticoagulants due to increased bleeding risk, unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs.
- XARELTO® should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A4 inhibitors (eg, diltiazem, verapamil, dronedarone, and erythromycin) unless the potential benefit justifies the potential risk.

### USE IN SPECIFIC POPULATIONS

- **Pregnancy Category C:** XARELTO® should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus. There are no adequate or well-controlled studies of XARELTO® in pregnant women, and dosing for pregnant women has not been established. Use XARELTO® with caution in pregnant patients because of the potential for pregnancy-related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO® cannot be reliably monitored with standard laboratory testing.

Xarelto®
rivaroxaban tablets

## IMPORTANT SAFETY INFORMATION (cont'd)

### USE IN SPECIFIC POPULATIONS (cont'd)

- **Labor and Delivery:** Safety and effectiveness of XARELTO® during labor and delivery have not been studied in clinical trials.
- **Nursing Mothers:** It is not known if rivaroxaban is excreted in human milk.
- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.
- **Females of Reproductive Potential:** Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

### OVERDOSAGE

- Discontinue XARELTO® and initiate appropriate therapy if bleeding complications associated with overdosage occur. A specific antidote for rivaroxaban is not available. The use of activated charcoal to reduce absorption in case of XARELTO® overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not expected to be dialyzable.

### ADVERSE REACTIONS IN CLINICAL STUDIES

- The most common adverse reactions with XARELTO® were bleeding complications.

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**Please see accompanying Brief Summary of full Prescribing Information, including Boxed WARNINGS, or visit www.XareltoHCP.com/PI.**


**References: 1.** Beyer-Westendorf J, Förster K, Pannach S, et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. *Blood.* 2014;124(6):955-962. **2.** Beyer-Westendorf J, Lützner J, Donath L, et al. Efficacy and safety of thromboprophylaxis with low-molecular-weight heparin or rivaroxaban in hip and knee replacement surgery. Findings from the ORTHO-TEP registry. *Thromb Haemost.* 2013;109(1):154-163. **3.** Ogawa S, Ikeda T, Kitazono T, et al; on behalf of the Rivaroxaban Postmarketing Surveillance Registry Investigators. Present profiles of novel anticoagulant use in Japanese patients with atrial fibrillation: insights from the rivaroxaban postmarketing surveillance registry. *J Stroke Cerebrovasc Dis.* 2014;23(10):2520-2526. **4.** Laliberté F, Cloutier M, Nelson WW, et al. Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. *Curr Med Res Opin.* 2014;30(7):1317-1325. **5.** Turpie AGG, Haas S, Kreutz R, et al. A non-interventional comparison of rivaroxaban with standard of care for thromboprophylaxis after major orthopaedic surgery in 17,701 patients with propensity score adjustment. *Thromb Haemost.* 2014; 111(1):94-102. **6.** Abraham NS, Singh S, Alexander CG, et al. Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study. *BMJ.* 2015;350:h1857. **7.** Chang H-Y, Zhou M, Tang W, Alexander GC, Singh S. Risk of gastrointestinal bleeding associated with oral anticoagulants: population based retrospective cohort study. *BMJ.* 2015;350:h1585. **8.** Lauffenburger JC, Farley JF, Gehi AK, Rhoney DH, Brookhart MA, Fang G. Factors driving anticoagulant selection in patients with atrial fibrillation in the United States. *Am J Cardiol.* 2015;115(8):1095-1101. **9.** Olesen JB, Sørensen R, Hansen ML, et al. Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naïve atrial fibrillation patients: Danish nationwide descriptive data 2011–2013. *Europace.* 2015;17(2):187-193. **10.** Camm AJ, Amarenco P, Haas S, et al. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur Heart J.* 2015;1-9. **11.** Tamayo S, Peacock WF, Patel M, et al. Characterizing major bleeding in patients with non-valvular atrial fibrillation: a pharmacovigilance study of 27,467 patients taking rivaroxaban. *Clin Cardiol.* 2015;38(2):63-68. **12.** Patel MR, Mahaffey KW, Garg J, et al; and the ROCKET AF Steering Committee, for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365(10):883-891.




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Brief Summary of Prescribing Information for XARELTO® (rivaroxaban)

**XARELTO®** (rivaroxaban) tablets, for oral use
See package insert for full Prescribing Information

**WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA**

**A. PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS**

**Premature discontinuation of any oral anticoagulant, including XARELTO, increases the risk of thrombotic events. If anticoagulation with XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.2, 2.6) in full Prescribing Information, Warnings and Precautions, and Clinical Studies (14.1) in full Prescribing Information].***

**B. SPINAL/EPIDURAL HEMATOMA**

**Epidural or spinal hematomas have occurred in patients treated with XARELTO who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:**

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of XARELTO and neuraxial procedures is not known**

***[see Warnings and Precautions and Adverse Reactions].***

**Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions].***

**Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis *[see Warnings and Precautions].***

## INDICATIONS AND USAGE

**Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation:** XARELTO is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

There are limited data on the relative effectiveness of XARELTO and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled *[see Clinical Studies (14.1) in full Prescribing Information].*

**Treatment of Deep Vein Thrombosis:** XARELTO is indicated for the treatment of deep vein thrombosis (DVT).

**Treatment of Pulmonary Embolism:** XARELTO is indicated for the treatment of pulmonary embolism (PE).

**Reduction in the Risk of Recurrence of Deep Vein Thrombosis and of Pulmonary Embolism:** XARELTO is indicated for the reduction in the risk of recurrence of deep vein thrombosis and of pulmonary embolism following initial 6 months treatment for DVT and/or PE.

**Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:** XARELTO is indicated for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.

## CONTRAINDICATIONS

XARELTO is contraindicated in patients with:

- active pathological bleeding *[see Warnings and Precautions]*
- severe hypersensitivity reaction to XARELTO (e.g., anaphylactic reactions) *[see Adverse Reactions]*

## WARNINGS AND PRECAUTIONS

**Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including XARELTO, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO to warfarin in clinical trials in atrial fibrillation patients. If XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.2, 2.6) and Clinical Studies (14.1) in full Prescribing Information].*

**Risk of Bleeding:** XARELTO increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe XARELTO to patients at increased risk of bleeding, the risk of thrombotic events should be weighed against the risk of bleeding.

Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue XARELTO in patients with active pathological hemorrhage. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

Concomitant use of other drugs that impair hemostasis increases the risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, and non-steroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions].*

Concomitant use of drugs that are combined P-gp and CYP3A4 inhibitors (e.g., ketoconazole and ritonavir) increases rivaroxaban exposure and may increase bleeding risk *[see Drug Interactions].*

*Reversal of Anticoagulant Effect:* A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable *[see Clinical Pharmacology (12.3) in full Prescribing Information].* Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Partial reversal of prothrombin time prolongation has been seen after administration of prothrombin complex concentrates (PCCs) in healthy volunteers. The use of other procoagulant reversal agents like activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (rFVIIa) has not been evaluated.

**Spinal/Epidural Anesthesia or Puncture:** When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an

epidural or spinal hematoma which can result in long-term or permanent paralysis *[see Boxed Warning]*.

To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

An epidural catheter should not be removed earlier than 18 hours after the last administration of XARELTO. The next XARELTO dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of XARELTO is to be delayed for 24 hours.

Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently to detect any signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), bowel and/or bladder dysfunction. Instruct patients to immediately report if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

**Use in Patients with Renal Impairment:** Nonvalvular Atrial Fibrillation: Avoid the use of XARELTO in patients with CrCl <15 mL/min since drug exposure is increased. Periodically assess renal function as clinically indicated (i.e., more frequently in situations in which renal function may decline) and adjust therapy accordingly. Discontinue XARELTO in patients who develop acute renal failure while on XARELTO *[see Use in Specific Populations]*

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE: Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population *[see Use in Specific Populations]*.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on XARELTO should discontinue the treatment *[see Use in Specific Populations]*.

**Use in Patients with Hepatic Impairment:** No clinical data are available for patients with severe hepatic impairment.

Avoid use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy since drug exposure and bleeding risk may be increased *[see Use in Specific Populations]*.

**Use with P-gp and Strong CYP3A4 Inhibitors or Inducers:** Avoid concomitant use of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir, and conivaptan) *[see Drug Interactions]*.

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) *[see Drug Interactions]*.

**Risk of Pregnancy-Related Hemorrhage:** In pregnant women, XARELTO should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).

**Patients with Prosthetic Heart Valves:** The safety and efficacy of XARELTO have not been studied in patients with prosthetic heart valves. Therefore, use of XARELTO is not recommended in these patients.

**Acute PE in Hemodynamically Unstable Patients or Patients Who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of XARELTO is not recommended acutely as an alternative to unfractionated heparin in patients with pulmonary embolism who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

## ADVERSE REACTIONS

The following adverse reactions are also discussed in other sections of the labeling:

- Increased risk of stroke after discontinuation in nonvalvular atrial fibrillation *[see Boxed Warning* and *Warnings and Precautions]*
- Bleeding risk *[see Warnings and Precautions]*
- Spinal/epidural hematoma *[see Boxed Warning* and *Warnings and Precautions]*

**Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During clinical development for the approved indications, 16326 patients were exposed to XARELTO. These included 7111 patients who received XARELTO 15 mg or 20 mg orally once daily for a mean of 19 months (5558 for 12 months and 2512 for 24 months) to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation (ROCKET AF); 4728 patients who received either XARELTO 15 mg orally twice daily for three weeks followed by 20 mg orally once daily (EINSTEIN DVT, EINSTEIN PE) or 20 mg orally once daily (EINSTEIN Extension) to treat DVT, PE, and to reduce the risk of recurrence of DVT and of PE; and 4487 patients who received XARELTO 10 mg orally once daily for prophylaxis of DVT following hip or knee replacement surgery (RECORD 1-3).

Hemorrhage: The most common adverse reactions with XARELTO were bleeding complications *[see Warnings and Precautions]*.

*Nonvalvular Atrial Fibrillation:* In the ROCKET AF trial, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 4.3% for XARELTO vs. 3.1% for warfarin. The incidence of discontinuations for non-bleeding adverse events was similar in both treatment groups.

**XARELTO®** (rivaroxaban) tablets

Table 1 shows the number of patients experiencing various types of bleeding events in the ROCKET AF trial.

**Table 1: Bleeding Events in ROCKET AF*- On Treatment Plus 2 Days**

| Parameter | XARELTO N = 7111 n (%/year) | Warfarin N = 7125 n (%/year) | XARELTO vs. Warfarin HR (95% CI) |
|---|---|---|---|
| Major Bleeding† | 395 (3.6) | 386 (3.5) | 1.04 (0.90, 1.20) |
| Intracranial Hemorrhage (ICH)‡ | 55 (0.5) | 84 (0.7) | 0.67 (0.47, 0.93) |
| Hemorrhagic Stroke§ | 36 (0.3) | 58 (0.5) | 0.63 (0.42, 0.96) |
| Other ICH | 19 (0.2) | 26 (0.2) | 0.74 (0.41, 1.34) |
| Gastrointestinal (GI)¶ | 221 (2.0) | 140 (1.2) | 1.61 (1.30, 1.99) |
| Fatal Bleeding# | 27 (0.2) | 55 (0.5) | 0.50 (0.31, 0.79) |
| ICH | 24 (0.2) | 42 (0.4) | 0.58 (0.35, 0.96) |
| Non-intracranial | 3 (0.0) | 13 (0.1) | 0.23 (0.07, 0.82) |

Abbreviations: HR = Hazard Ratio, CI = Confidence interval, CRNM = Clinically Relevant Non-Major.

* Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment.

† Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥2 g/dL, a transfusion of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome.

‡ Intracranial bleeding events included intraparenchymal, intraventricular, subdural, subarachnoid and/or epidural hematoma.

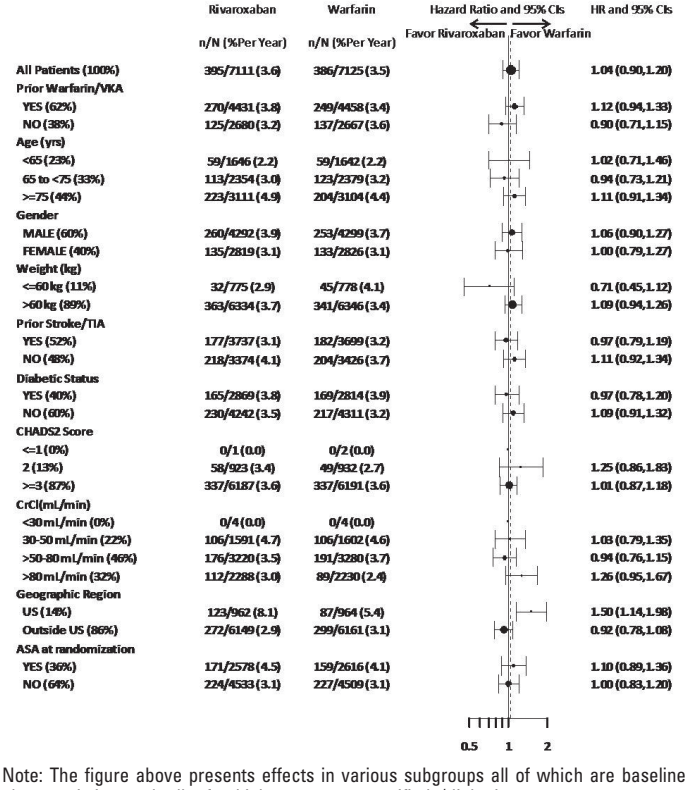
§ Hemorrhagic stroke in this table specifically refers to non-traumatic intraparenchymal and/or intraventricular hematoma in patients on treatment plus 2 days.

¶ Gastrointestinal bleeding events included upper GI, lower GI, and rectal bleeding.

# Fatal bleeding is adjudicated death with the primary cause of death from bleeding.

Figure 1 shows the risk of major bleeding events across major subgroups.

**Figure 1: Risk of Major Bleeding Events by Baseline Characteristics in ROCKET AF – On Treatment Plus 2 Days**




Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified (diabetic status was not pre-specified in the subgroup, but was a criterion for the CHADS2 score). The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

*Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and to Reduce the Risk of Recurrence of DVT and of PE:* EINSTEIN DVT and EINSTEIN PE Studies: In the pooled analysis of the EINSTEIN DVT and EINSTEIN PE clinical studies, the most frequent adverse reactions leading to permanent drug discontinuation were bleeding events, with XARELTO vs. enoxaparin/Vitamin K antagonist (VKA) incidence rates of 1.7% vs. 1.5%, respectively. The mean duration of treatment was 208 days for XARELTO-treated patients and 204 days for enoxaparin/VKA-treated patients.

Table 2 shows the number of patients experiencing major bleeding events in the pooled analysis of the EINSTEIN DVT and EINSTEIN PE studies.

**Table 2: Bleeding Events* in the Pooled Analysis of EINSTEIN DVT and EINSTEIN PE Studies**

| Parameter | XARELTO† N = 4130 n (%) | Enoxaparin/ VKA† N = 4116 n (%) |
|---|---|---|
| Major bleeding event | 40 (1.0) | 72 (1.7) |
| Fatal bleeding | 3 (<0.1) | 8 (0.2) |
| Intracranial | 2 (<0.1) | 4 (<0.1) |
| Non-fatal critical organ bleeding | 10 (0.2) | 29 (0.7) |
| Intracranial‡ | 3 (<0.1) | 10 (0.2) |
| Retroperitoneal‡ | 1 (<0.1) | 8 (0.2) |
| Intraocular‡ | 3 (<0.1) | 2 (<0.1) |
| Intra-articular‡ | 0 | 4 (<0.1) |
| Non-fatal non-critical organ bleeding§ | 27 (0.7) | 37 (0.9) |
| Decrease in Hb ≥ 2g/dL | 28 (0.7) | 42 (1.0) |
| Transfusion of ≥2 units of whole blood or packed red blood cells | 18 (0.4) | 25 (0.6) |
| Clinically relevant non-major bleeding | 357 (8.6) | 357 (8.7) |
| Any bleeding | 1169 (28.3) | 1153 (28.0) |

* Bleeding event occurred after randomization and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.

† Treatment schedule in EINSTEIN DVT and EINSTEIN PE studies: XARELTO 15 mg twice daily for 3 weeks followed by 20 mg once daily; enoxaparin/VKA [enoxaparin: 1 mg/kg twice daily, VKA: individually titrated doses to achieve a target INR of 2.5 (range: 2.0-3.0)]

‡ Treatment-emergent major bleeding events with at least >2 subjects in any pooled treatment group

§ Major bleeding which is not fatal or in a critical organ, but resulting in a decrease in Hb ≥2 g/dL and/or transfusion of ≥2 units of whole blood or packed red blood cells

EINSTEIN Extension Study: In the EINSTEIN Extension clinical study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 1.8% for XARELTO vs. 0.2% for placebo treatment groups. The mean duration of treatment was 190 days for both XARELTO and placebo treatment groups.

Table 3 shows the number of patients experiencing bleeding events in the EINSTEIN Extension study.

**Table 3: Bleeding Events* in EINSTEIN Extension Study**

| Parameter | XARELTO† 20 mg N = 598 n (%) | Placebo† N = 590 n (%) |
|---|---|---|
| Major bleeding event‡ | 4 (0.7) | 0 |
| Decrease in Hb ≥2 g/dL | 4 (0.7) | 0 |
| Transfusion of ≥2 units of whole blood or packed red blood cells | 2 (0.3) | 0 |
| Gastrointestinal | 3 (0.5) | 0 |
| Menorrhagia | 1 (0.2) | 0 |
| Clinically relevant non-major bleeding | 32 (5.4) | 7 (1.2) |
| Any bleeding | 104 (17.4) | 63 (10.7) |

* Bleeding event occurred after the first dose and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.

† Treatment schedule: XARELTO 20 mg once daily; matched placebo once daily

‡ There were no fatal or critical organ bleeding events.

*Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:* In the RECORD clinical trials, the overall incidence rate of adverse reactions leading to permanent treatment discontinuation was 3.7% with XARELTO.

The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown in Table 4.

**Table 4: Bleeding Events* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1-3)**

| | XARELTO 10 mg | Enoxaparin† |
|---|---|---|
| **Total treated patients** | **N = 4487 n (%)** | **N = 4524 n (%)** |
| Major bleeding event | 14 (0.3) | 9 (0.2) |
| Fatal bleeding | 1 (<0.1) | 0 |
| Bleeding into a critical organ | 2 (<0.1) | 3 (0.1) |
| Bleeding that required re-operation | 7 (0.2) | 5 (0.1) |
| Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells | 4 (0.1) | 1 (<0.1) |
| Any bleeding event‡ | 261 (5.8) | 251 (5.6) |



**Table 4: Bleeding Events* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1-3) (continued)**

| | XARELTO 10 mg | Enoxaparin† |
|---|---|---|
| **Hip Surgery Studies** | **N = 3281 n (%)** | **N = 3298 n (%)** |
| Major bleeding event | 7 (0.2) | 3 (0.1) |
| Fatal bleeding | 1 (<0.1) | 0 |
| Bleeding into a critical organ | 1 (<0.1) | 1 (<0.1) |
| Bleeding that required re-operation | 2 (0.1) | 1 (<0.1) |
| Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells | 3 (0.1) | 1 (<0.1) |
| Any bleeding event‡ | 201 (6.1) | 191 (5.8) |
| **Knee Surgery Study** | **N = 1206 n (%)** | **N = 1226 n (%)** |
| Major bleeding event | 7 (0.6) | 6 (0.5) |
| Fatal bleeding | 0 | 0 |
| Bleeding into a critical organ | 1 (0.1) | 2 (0.2) |
| Bleeding that required re-operation | 5 (0.4) | 4 (0.3) |
| Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells | 1 (0.1) | 0 |
| Any bleeding event‡ | 60 (5.0) | 60 (4.9) |

* Bleeding events occurring any time following the first dose of double-blind study medication (which may have been prior to administration of active drug) until two days after the last dose of double-blind study medication. Patients may have more than one event.

† Includes the placebo-controlled period for RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

‡ Includes major bleeding events

Following XARELTO treatment, the majority of major bleeding complications (≥60%) occurred during the first week after surgery.

Other Adverse Reactions: Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in the EINSTEIN Extension study are shown in Table 5.

**Table 5: Other Adverse Reactions* Reported by ≥1% of XARELTO-Treated Patients in EINSTEIN Extension Study**

| System Organ Class<br>Preferred Term | XARELTO N = 598 n (%) | Placebo N = 590 n (%) |
|---|---|---|
| **Gastrointestinal disorders** | | |
| Abdominal pain upper | 10 (1.7) | 1 (0.2) |
| Dyspepsia | 8 (1.3) | 4 (0.7) |
| Toothache | 6 (1.0) | 0 |
| **General disorders and administration site conditions** | | |
| Fatigue | 6 (1.0) | 3 (0.5) |
| **Infections and infestations** | | |
| Sinusitis | 7 (1.2) | 3 (0.5) |
| Urinary tract infection | 7 (1.2) | 3 (0.5) |
| **Musculoskeletal and connective tissue disorders** | | |
| Back pain | 22 (3.7) | 7 (1.2) |
| Osteoarthritis | 10 (1.7) | 5 (0.8) |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Oropharyngeal pain | 6 (1.0) | 2 (0.3) |

* Adverse reaction (with Relative Risk >1.5 for XARELTO versus placebo) occurred after the first dose and up to 2 days after the last dose of study drug. Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical adverse reactions, the patient is counted only once in a category. The same patient may appear in different categories.

Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in RECORD 1-3 studies are shown in Table 6.

**Table 6: Other Adverse Drug Reactions* Reported by ≥1% of XARELTO-Treated Patients in RECORD 1-3 Studies**

| System/Organ Class<br>Adverse Reaction | XARELTO 10 mg N = 4487 n (%) | Enoxaparin† N = 4524 n (%) |
|---|---|---|
| **Injury, poisoning and procedural complications** | | |
| Wound secretion | 125 (2.8) | 89 (2.0) |
| **Musculoskeletal and connective tissue disorders** | | |
| Pain in extremity | 74 (1.7) | 55 (1.2) |
| Muscle spasm | 52 (1.2) | 32 (0.7) |
| **Nervous system disorders** | | |
| Syncope | 55 (1.2) | 32 (0.7) |

**Table 6: Other Adverse Drug Reactions* Reported by ≥1% of XARELTO-Treated Patients in RECORD 1-3 Studies (continued)**

| System/Organ Class<br>Adverse Reaction | XARELTO 10 mg N = 4487 n (%) | Enoxaparin† N = 4524 n (%) |
|---|---|---|
| **Skin and subcutaneous tissue disorders** | | |
| Pruritus | 96 (2.1) | 79 (1.8) |
| Blister | 63 (1.4) | 40 (0.9) |

* Adverse reaction occurring any time following the first dose of double-blind medication, which may have been prior to administration of active drug, until two days after the last dose of double-blind study medication

† Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

*Other clinical trial experience:* In an investigational study of acute medically ill patients being treated with XARELTO 10 mg tablets, cases of pulmonary hemorrhage and pulmonary hemorrhage with bronchiectasis were observed.

**Postmarketing Experience:** The following adverse reactions have been identified during post-approval use of rivaroxaban. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Blood and lymphatic system disorders:* agranulocytosis, thrombocytopenia

*Gastrointestinal disorders:* retroperitoneal hemorrhage

*Hepatobiliary disorders:* jaundice, cholestasis, hepatitis (including hepatocellular injury)

*Immune system disorders:* hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema

*Nervous system disorders:* cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis

*Skin and subcutaneous tissue disorders:* Stevens-Johnson syndrome

**DRUG INTERACTIONS**

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors and inducers of these CYP450 enzymes or transporters (e.g., P-gp) may result in changes in rivaroxaban exposure.

**Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems:** In drug interaction studies, conducted in subjects with normal renal function, evaluating the concomitant use with drugs that are combined P-gp and CYP3A4 inhibitors (ketoconazole, ritonavir, clarithromycin, and erythromycin) or a moderate CYP3A4 inhibitor (fluconazole), increases in rivaroxaban exposure and pharmacodynamic effects (i.e., factor Xa inhibition and PT prolongation) were observed. The increases in exposure ranged from 30% to 160%. Significant increases in rivaroxaban exposure may increase bleeding risk *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

When data suggest a change in exposure is unlikely to affect bleeding risk (e.g., clarithromycin, erythromycin), no precautions are necessary during coadministration with drugs that are combined P-gp and CYP3A4 inhibitors.

Avoid concomitant administration of XARELTO with combined P-gp and strong CYP3A4 inhibitors *[see Warnings and Precautions]*.

**Drugs that Induce Cytochrome P450 3A4 Enzymes and Drug Transport Systems:** Results from drug interaction studies and population PK analyses from clinical studies indicate coadministration of XARELTO with a combined P-gp and strong CYP3A4 inducer (e.g., rifampicin, phenytoin) decreased rivaroxaban exposure by up to 50%. Similar decreases in pharmacodynamic effects were also observed. These decreases in exposure to rivaroxaban may decrease efficacy *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) *[see Warnings and Precautions]*.

**Anticoagulants and NSAIDs/Aspirin:** Single doses of enoxaparin and XARELTO given concomitantly resulted in an additive effect on anti-factor Xa activity. Single doses of warfarin and XARELTO resulted in an additive effect on factor Xa (FXa) inhibition and PT. Concomitant aspirin use has been identified as an independent risk factor for major bleeding in efficacy trials. NSAIDs are known to increase bleeding, and bleeding risk may be increased when NSAIDs are used concomitantly with XARELTO. Coadministration of the platelet aggregation inhibitor clopidogrel and XARELTO resulted in an increase in bleeding time for some subjects *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Avoid concurrent use of XARELTO with other anticoagulants due to increased bleeding risk unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs *[see Warnings and Precautions]*.

**Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems:** Results from a pharmacokinetic trial with erythromycin indicated that patients with renal impairment coadministered XARELTO with drugs classified as combined P-gp and moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, dronedarone, and erythromycin) have increased exposure compared with patients with normal renal function and no inhibitor use. Significant increases in rivaroxaban exposure may increase bleeding risk.

While increases in rivaroxaban exposure can be expected under such conditions, results from an analysis in the ROCKET AF trial, which allowed concomitant use with either combined P-gp and/or weak or moderate CYP3A4 inhibitors (e.g., amiodarone, diltiazem, verapamil, chloramphenicol, cimetidine, and erythromycin), did not show an increase in bleeding in patients with CrCl 30 to <50 mL/min [Hazard Ratio (95% CI): 1.05 (0.77, 1.42)] *[see Use in Specific Populations]*.

XARELTO should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, dronedarone, and erythromycin) unless the potential benefit justifies the potential risk *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

**XARELTO®** (rivaroxaban) tablets

**USE IN SPECIFIC POPULATIONS**

**Pregnancy:** Pregnancy Category C: There are no adequate or well-controlled studies of XARELTO in pregnant women, and dosing for pregnant women has not been established. Use XARELTO with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO cannot be reliably monitored with standard laboratory testing. Animal reproduction studies showed no increased risk of structural malformations, but increased post-implantation pregnancy loss occurred in rabbits. XARELTO should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus *[see Warnings and Precautions]*.

Rivaroxaban crosses the placenta in animals. Animal reproduction studies have shown pronounced maternal hemorrhagic complications in rats and an increased incidence of post-implantation pregnancy loss in rabbits. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant rabbits were given oral doses of ≥10 mg/kg rivaroxaban during the period of organogenesis. This dose corresponds to about 4 times the human exposure of unbound drug, based on AUC comparisons at the highest recommended human dose of 20 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg. This dose corresponds to about 14 times the human exposure of unbound drug.

**Labor and Delivery:** Safety and effectiveness of XARELTO during labor and delivery have not been studied in clinical trials. However, in animal studies maternal bleeding and maternal and fetal death occurred at the rivaroxaban dose of 40 mg/kg (about 6 times maximum human exposure of the unbound drug at the human dose of 20 mg/day).

**Nursing Mothers:** It is not known if rivaroxaban is excreted in human milk. Rivaroxaban and/or its metabolites were excreted into the milk of rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rivaroxaban, a decision should be made whether to discontinue nursing or discontinue XARELTO, taking into account the importance of the drug to the mother.

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use:** Of the total number of patients in the RECORD 1-3 clinical studies evaluating XARELTO, about 54% were 65 years and over, while about 15% were >75 years. In ROCKET AF, approximately 77% were 65 years and over and about 38% were >75 years. In the EINSTEIN DVT, PE and Extension clinical studies approximately 37% were 65 years and over and about 16% were >75 years. In clinical trials the efficacy of XARELTO in the elderly (65 years or older) was similar to that seen in patients younger than 65 years. Both thrombotic and bleeding event rates were higher in these older patients, but the risk-benefit profile was favorable in all age groups *[see Clinical Pharmacology (12.3) and Clinical Studies (14) in full Prescribing Information]*.

**Females of Reproductive Potential:** Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

**Renal Impairment:** In a pharmacokinetic study, compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased by approximately 44 to 64% in subjects with renal impairment. Increases in pharmacodynamic effects were also observed *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Nonvalvular Atrial Fibrillation: In the ROCKET AF trial, patients with CrCl 30 to 50 mL/min were administered XARELTO 15 mg once daily resulting in serum concentrations of rivaroxaban and clinical outcomes similar to those in patients with better renal function administered XARELTO 20 mg once daily. Patients with CrCl 15 to 30 mL/min were not studied, but administration of XARELTO 15 mg once daily is also expected to result in serum concentrations of rivaroxaban similar to those in patients with normal renal function *[see Dosage and Administration (2.3) in full Prescribing Information]*.

Treatment of DVT and/or PE, and Reduction in the Risk of Recurrence of DVT and of PE: In the EINSTEIN trials, patients with CrCl values <30 mL/min at screening were excluded from the studies. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

Prophylaxis of DVT Following Hip or Knee Replacement Surgery: The combined analysis of the RECORD 1-3 clinical efficacy studies did not show an increase in bleeding risk for patients with CrCl 30 to 50 mL/min and reported a possible increase in total venous thromboemboli in this population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

**Hepatic Impairment:** In a pharmacokinetic study, compared to healthy subjects with normal liver function, AUC increases of 127% were observed in subjects with moderate hepatic impairment (Child-Pugh B).

The safety or PK of XARELTO in patients with severe hepatic impairment (Child-Pugh C) has not been evaluated *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Avoid the use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.

**OVERDOSAGE:**

Overdose of XARELTO may lead to hemorrhage. Discontinue XARELTO and initiate appropriate therapy if bleeding complications associated with overdosage occur. A specific antidote for rivaroxaban is not available. Rivaroxaban systemic exposure is not further increased at single doses >50 mg due to limited absorption. The use of activated charcoal to reduce absorption in case of XARELTO overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not expected to be dialyzable *[see Warnings and Precautions and Clinical Pharmacology (12.3) in full Prescribing Information]*. Partial reversal of laboratory anticoagulation parameters may be achieved with use of plasma products.

Active Ingredient Made in Germany

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