



Pediatric VTE and post-Fontan care are complex.^{1,2}

Helping protect against thrombosis doesn't have to be.

FDA APPROVED with 2 indications in pediatric patients³

For use in children aged birth to <18 years to treat VTE and reduce the risk of recurrence³



For use in children aged ≥2 years with congenital heart disease as thromboprophylaxis post-Fontan procedure³



XARELTO®: the direct oral anticoagulant (DOAC) studied in the largest clinical trials for pediatric VTE treatment and prevention (N=500) and for pediatric patients post-Fontan procedure (N=110)⁴⁻⁸

INDICATIONS

XARELTO® is indicated for the treatment of venous thromboembolism (VTE) and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years after at least 5 days of initial parenteral anticoagulant treatment.

XARELTO® is indicated for thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure.

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.

Please read additional Important Safety Information on the following pages and full [Prescribing Information](#) including **Boxed WARNINGS** for XARELTO®.

References: 1. Monagle P, Cuello CA, Augustine C, et al. American Society of Hematology 2018 Guidelines for Management of Venous Thromboembolism: treatment of pediatric venous thromboembolism. *Blood Adv.* 2018;2(22):3292-3316. DOI: 10.1182/bloodadvances.2018024828 2. Giglia TM, Massicotte MP, Tweddell JS, et al. Prevention and treatment of thrombosis in pediatric and congenital heart disease. A scientific statement from the American Heart Association. *Circulation.* 2013;128(24):2622-2703. DOI: 10.1161/01.cir.0000436140.77832.7a 3. XARELTO® [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 4. Male C, Lensing AWA, Palumbo JS, et al; EINSTEIN-Jr Phase 3 Investigators. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. *Lancet Haematol.* 2019;7(11):e18-e27. 5. ClinicalTrials.gov. NCT01895777. Open label study comparing efficacy and safety of dabigatran etexilate to standard of care in paediatric patients with venous thromboembolism (VTE). Accessed May 2, 2022. 6. ClinicalTrials.gov. NCT02464969. Apixaban for the acute treatment of venous thromboembolism in children. Accessed May 2, 2022. 7. ClinicalTrials.gov. NCT02798471. Hokusai study in pediatric patients with confirmed venous thromboembolism (VTE). Accessed November 3, 2021. 8. McCrindle BW, Michelson AD, Van Bergen AH, et al; UNIVERSE Study Investigators. Thromboprophylaxis for children post-Fontan procedure: insights from the UNIVERSE study. *J Am Heart Assoc.* 2021;e021765. doi:10.1161/JAHA.120.021765



Clinical Trials

Safety Profile

Efficacy Profile

For treatment and reduction of recurrence of VTE in pediatric patients from birth to <18 years of age

Dosing & Administration

Summary



XARELTO[®], studied in the EINSTEIN-Jr clinical trial, is the

Only DOAC FDA APPROVED to treat VTE and reduce risk of recurrence in children from birth to <18 years of age¹⁻³

XARELTO[®] is indicated for the treatment of VTE and the reduction in the risk of recurrent VTE in pediatric patients from birth to <18 years, after ≥5 days of initial parenteral anticoagulant treatment.

[View Clinical Trial](#)

DOAC = direct oral anticoagulant.

IMPORTANT SAFETY INFORMATION (cont'd)

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.

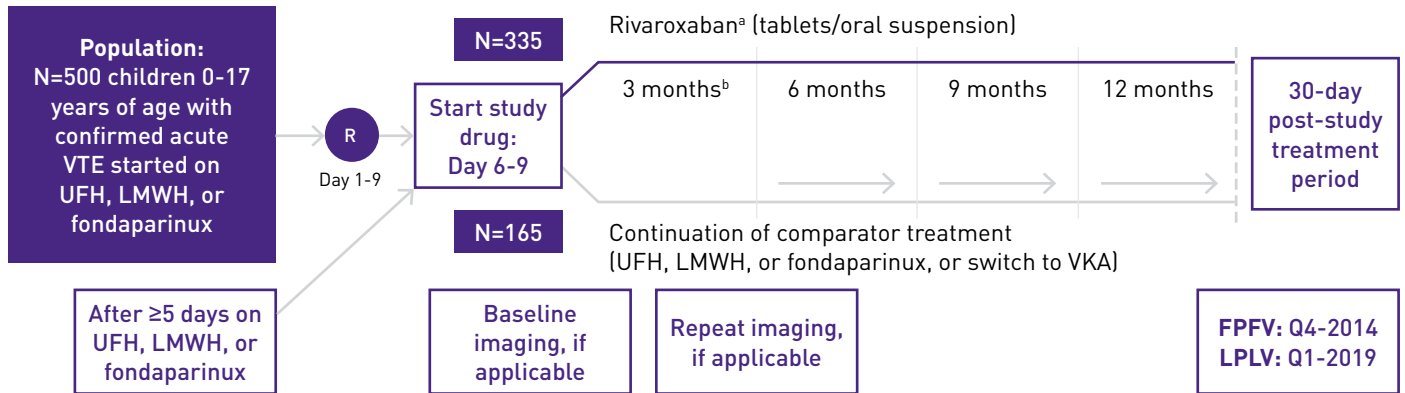
Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

Please read additional Important Safety Information on the following pages and full [Prescribing Information](#) including **Boxed WARNINGS** for XARELTO[®].

In the EINSTEIN-Jr clinical trial

The largest pediatric DOAC trial conducted for the treatment of VTE and the first to evaluate a liquid formulation in this population¹⁻⁶

Objective | A randomized, multicenter, active-controlled, open-label, phase 3 trial to evaluate XARELTO® vs comparator* for treatment of acute VTE in a pediatric population^{3,7}



Not powered for noninferiority due to the low incidence of VTE in children and the lack of well-documented information on recurrence and treatment effect with standard anticoagulants in children; hence, there was no formal a priori sample size calculation.³

^aBodyweight-adjusted rivaroxaban dose equivalent to 20 mg once daily adult dose.
^bChildren aged <2 years with CVC-VTE: extension with maximum 2 blocks of 1 month, maximum duration of 3 months; decision to stop or continue treatment made after each 3- or 1-month block.
^cComparator treatment = UFH, LMWH, fondaparinux, or VKA.
 CVC-VTE = central venous catheter-related VTE; DOAC = direct oral anticoagulant; PPFV = first patient first visit; LMWH = low-molecular-weight heparin; LPLV = last patient last visit; UFH = unfractionated heparin; VKA = vitamin K antagonist.

IMPORTANT SAFETY INFORMATION (cont'd)

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to XARELTO® (eg, anaphylactic 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.
- **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 in patients with active pathological hemorrhage.
 - An agent to reverse the anti-factor Xa activity of rivaroxaban is available. Because of high plasma protein binding, rivaroxaban is not dialyzable.

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**Clinical Trial****Safety Profile****Efficacy Profile**

For treatment and reduction of recurrence of VTE in pediatric patients from birth to <18 years of age

Dosing & Administration**Summary**

EINSTEIN-Jr clinical trial study design^{3,7}

STUDY POPULATION

Children aged 0 to 17 years of age with acute VTE initially started on UFH, LMWH, or fondaparinux for ≥5 days before randomization

TREATMENT GROUPS

- Randomized in a 2:1 ratio to XARELTO® (n=335) or comparator (n=165), stratified by age and VTE site
 - XARELTO® administered as tablets or oral suspension and weight adjusted to achieve drug exposure comparable to 20 mg/day in adults
 - Standard anticoagulation*: continued heparin treatment or switched to a vitamin K antagonist
- Main treatment duration: 3 months, or 1 month in children <2 years with catheter-related VTE
 - With the option to continue treatment in 3-month increments up to a maximum of 12 months, with the exception of children <2 years of age with CVC-VTE who were treated with XARELTO® in 1-month increments up to a maximum of 3 months

OUTCOMES

- Primary efficacy outcome: symptomatic recurrent VTE in ITT population
- Secondary efficacy outcomes:
 - Composite of recurrent VTE and deterioration on repeated vascular (clot) imaging
- Principal safety outcome: composite of overt major bleeding and clinically relevant nonmajor bleeding[†]

Not powered for noninferiority due to the low incidence of VTE in children and the lack of well-documented information on recurrence and treatment effect with standard anticoagulants in children; hence, there was no formal a priori sample size calculation.^{3‡}

*Comparators were given at therapeutic doses, according to international guidelines, and included UFH, LMWH, or fondaparinux. Following completion of 5 to 9 days of standard anticoagulation, participants continued with heparin treatment or were switched to a VKA at the discretion of the treating physician for a main study treatment period of 3 months (or 1 month for children <2 years with CVC-VTE). A diagnostic imaging test was obtained at baseline and at the end of the main study treatment. When clinically necessary, treatment was extended up to 12 months in total (or up to 3 months in total for children <2 years with CVC-VTE.)^{1,3,7}

[†]Clinically relevant nonmajor bleeding is clinically overt bleeding, which did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact with a physician, temporary cessation of treatment, discomfort for the patient, or impairment of activities of daily life. Major bleeding is 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.

[‡]The study could not be powered to independently show noninferiority for efficacy of rivaroxaban in comparison to standard therapy in children; therefore, interpretation of the results relies in part on extrapolation of data obtained with rivaroxaban in adults; hence, there was no formal a priori sample size calculation.

CVC-VTE = central venous catheter-related VTE; ITT = intent-to-treat; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist.

Patient Population Baseline Characteristics ↗

IMPORTANT SAFETY INFORMATION (cont'd) WARNINGS AND PRECAUTIONS (cont'd)

- **Risk of Bleeding (cont'd):**
 - Concomitant use of other drugs that impair hemostasis increases risk of bleeding. These include aspirin, P2Y₁₂ platelet inhibitors, dual antiplatelet therapy, other antithrombotic agents, fibrinolytic therapy, NSAIDs, selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs).
 - **Risk of Hemorrhage in Acutely Ill Medical Patients at High Risk of Bleeding:** Acutely ill medical patients with the following conditions are at increased risk of bleeding with the use of XARELTO® for primary VTE prophylaxis: history of bronchiectasis, pulmonary cavitation, or pulmonary hemorrhage; active cancer (ie, undergoing acute, in-hospital cancer treatment); active gastroduodenal ulcer or history of bleeding in the three months prior to treatment; or dual antiplatelet therapy. XARELTO® is not for use for primary VTE prophylaxis in these hospitalized, acutely ill medical patients at high risk of bleeding.

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Patient Population Baseline Characteristics³

	Age birth–23 months		Age 2–5 years		Age 6–11 years		Age 12–17 years		Total	
	Rivaroxaban (n=37)	Comparator (n=17)	Rivaroxaban (n=47)	Comparator (n=22)	Rivaroxaban (n=67)	Comparator (n=34)	Rivaroxaban (n=184)	Comparator (n=92)	Rivaroxaban (n=335)	Comparator (n=165)
Sex										
Female	15 (41%)	6 (35%)	24 (51%)	9 (41%)	24 (36%)	15 (44%)	97 (53%)	55 (60%)	160 (48%)	85 (52%)
Male	22 (59%)	11 (65%)	23 (49%)	13 (59%)	43 (64%)	19 (56%)	87 (47%)	37 (40%)	175 (52%)	80 (48%)
Race										
Caucasian	22 (59%)	11 (65%)	40 (85%)	17 (77%)	51 (76%)	23 (68%)	158 (86%)	73 (79%)	271 (81%)	124 (75%)
Asian	6 (16%)	3 (18%)	2 (4%)	2 (9%)	9 (13%)	1 (3%)	3 (2%)	2 (2%)	20 (6%)	8 (5%)
Black	3 (8%)	0	1 (2%)	0	2 (3%)	4 (12%)	7 (4%)	8 (9%)	13 (4%)	12 (7%)
Other or not disclosed	6 (16%)	3 (18%)	4 (9%)	3 (14%)	5 (7%)	6 (18%)	16 (9%)	10 (11%)	31 (9%)	21 (13%)
Bodyweight, range, kg	2-7-15	3-0-14	10-25	8-6-22	17-71	19-72	27-135	32-160	2-7-135	3-0-160
Index venous thrombosis location										
Cerebral vein or sinus thrombosis	4 (11%)	5 (29%)	23 (49%)	12 (55%)	31 (46%)	17 (50%)	16 (9%)	9 (10%)	74 (22%)	43 (26%)
Catheter-related venous thromboembolism	26 (70%)	11 (65%)	19 (40%)	7 (32%)	16 (24%)	8 (24%)	29 (16%)	11 (12%)	90 (27%)	37 (22%)
Lower extremities	13/26 (50%)	9/11 (82%)	6/19 (32%)	4/7 (57%)	2/16 (13%)	2/8 (25%)	1/29 (3%)	0	22/90 (24%)	15/37 (41%)
Caval, renal, or portal vein	0	1/11 (9%)	0	0	1/16 (6%)	0	1/29 (3%)	0	2/90 (2%)	1/37 (3%)
Right heart	1/26 (4%)	0	2/19 (11%)	1/7 (14%)	2/16 (13%)	2/8 (25%)	2/29 (7%)	1/11 (9%)	7/90 (8%)	4/37 (11%)
Upper extremities*	0	0	4/19 (21%)	0	5/16 (31%)	2/8 (25%)	18/29 (62%)	6/11 (55%)	27/90 (30%)	8/37 (22%)
Jugular vein	12/26 (46%)	1/11 (9%)	7/19 (37%)	2/7 (29%)	6/16 (38%)	2/8 (25%)	7/29 (24%)	4/11 (36%)	32/90 (36%)	9/37 (24%)
Non-catheter-related venous thromboembolism	7 (19%)	1 (6%)	5 (11%)	3 (14%)	20 (30%)	9 (26%)	139 (76%)	72 (78%)	171 (51%)	85 (52%)
Lower extremities	2/7 (29%)	0	3/5 (60%)	1/3 (33%)	9/20 (45%)	6/9 (67%)	76/139 (55%)	31/72 (43%)	90/171 (53%)	38/85 (45%)
Caval, renal, or portal vein	4/7 (57%)	0	1/5 (20%)	0	3/20 (15%)	1/9 (11%)	2/139 (1%)	0	10/171 (6%)	1/85 (1%)
Right heart	0	0	0	0	1/20 (5%)	0	1/139 (1%)	1/72 (1%)	2/171 (1%)	1/85 (1%)
Pulmonary	0	0	0	2/3 (67%)	3/20 (15%)	0	46/139 (33%)	29/72 (40%)	49/171 (29%)	31/85 (36%)
Upper extremities*	0	1/1 (100%)	0	0	2/20 (10%)	2/9 (22%)	9/139 (6%)	9/72 (13%)	11/171 (6%)	12/85 (14%)
Jugular vein	1/7 (14%)	0	1/5 (20%)	0	2/20 (10%)	0	5/139 (4%)	2/72 (3%)	9/171 (5%)	2/85 (2%)
Symptomatic venous thromboembolism	20 (54%)	13 (76%)	32 (68%)	15 (68%)	50 (75%)	26 (76%)	169 (92%)	82 (89%)	271 (81%)	136 (82%)
First episode of venous thromboembolism	37 (100%)	16 (94%)	44 (94%)	21 (95%)	65 (97%)	32 (94%)	180 (98%)	83 (90%)	326 (97%)	152 (92%)
Initial heparinisation †	37 (100%)	17 (100%)	47 (100%)	22 (100%)	67 (100%)	34 (100%)	184 (100%)	92 (100%)	335 (100%)	165 (100%)
Plus thrombolysis or thrombectomy, or both	0	0	3 (6%)	0	4 (6%)	1 (3%)	13 (7%)	5 (5%)	20 (6%)	6 (4%)
Rivaroxaban formulation										
Tablet	0	NA	1 (2%)	NA	18 (27%)	NA	106 (58%)	NA	125 (37%)	NA
Suspension	36 (97%)	NA	45 (96%)	NA	49 (73%)	NA	74 (40%)	NA	204 (60%)	NA
No study medication given	1 (3%)	NA	1 (2%)	NA	0	NA	4 (2%)	NA	6 (2%)	NA
Standard anticoagulation group										
Heparins † only	NA	15 (88%)	NA	17 (77%)	NA	26 (76%)	NA	48 (52%)	NA	106 (64%)
Heparins and vitamin K antagonist	NA	2 (12%)	NA	5 (23%)	NA	8 (24%)	NA	41 (45%)	NA	56 (34%)
No study medication given	NA	0	NA	0	NA	0	NA	3 (3%)	NA	3 (2%)
Study treatment duration, days										
3-month intended study period	91 (83-96)	89 (84-91)	92 (89-96)	92 (90-95)	91 (87-95)	92 (89-93)	91 (88-95)	90 (85-94)	91 (88-95)	91 (87-94)
1-month intended study period	32 (29-35)	29 (28-31)	NA	NA	NA	NA	NA	NA	NA	NA

Data are n (%) or median (IQR). NA=not applicable. *Including axillary and subclavian vein. †Unfractionated heparin, low molecular weight heparin, or fondaparinux.

Table 1: Baseline characteristics

inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs).

Risk of Hemorrhage in Acutely Ill Medical Patients at High Risk of Bleeding: Acutely ill medical conditions are at increased risk of bleeding with the use of XARELTO[®] for primary VTE prophylaxis in hospitalized, acutely ill medical patients at high risk of bleeding, including those with pulmonary cavitation, or pulmonary hemorrhage; active cancer (ie, undergoing acute, life-threatening chemotherapy); active or history of gastrointestinal ulcer or history of bleeding in the three months prior to treatment; or dual antiplatelet therapy. XARELTO[®] is not for use for primary VTE prophylaxis in these hospitalized, acutely ill medical patients at high risk of bleeding.

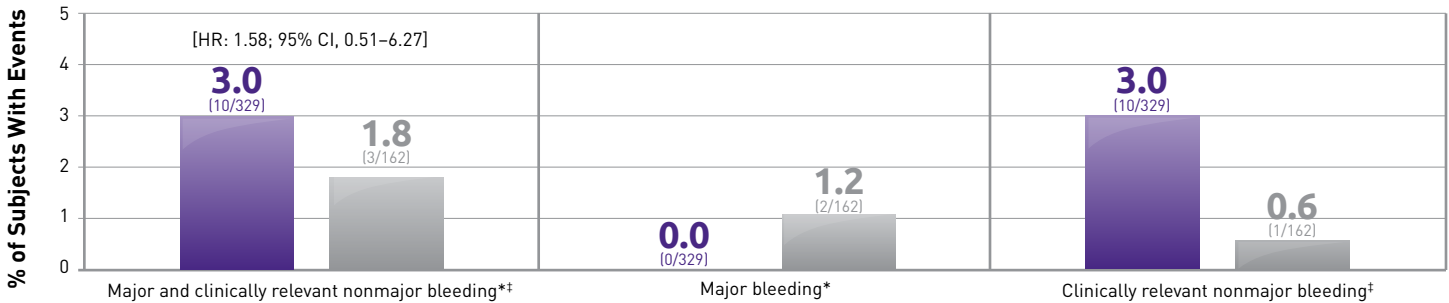


In the EINSTEIN-Jr clinical trial

XARELTO® demonstrated similar rates of major and clinically relevant nonmajor bleeding vs standard anticoagulation^{1*†‡}

Principal safety outcome

XARELTO® Comparator



[Additional Adverse Events Summary ↗](#)

Not powered for noninferiority due to the low incidence of VTE in children and the lack of well-documented information on recurrence and treatment effect with standard anticoagulants in children; hence, there was no formal a priori sample size calculation.³

*Major bleeding is 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.

†Comparators were given at therapeutic doses, according to international guidelines, and included UFH, LMWH, or fondaparinux. Following completion of 5 to 9 days of standard anticoagulation, participants continued with heparin treatment or were switched to a VKA at the discretion of the treating physician for a main study treatment period of 3 months (or 1 month for children <2 years with CVC-VTE). A diagnostic imaging test was obtained at baseline and at the end of the main study treatment. When clinically necessary, treatment was extended up to 12 months in total (or up to 3 months in total for children <2 years with CVC-VTE).^{1,3,7}

‡Clinically relevant nonmajor bleeding is clinically overt bleeding, which did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact with a physician, temporary cessation of treatment, discomfort for the patient, or impairment of activities of daily life.

CVC-VTE = central venous catheter-related VTE; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist.

IMPORTANT SAFETY INFORMATION (cont'd) WARNINGS AND PRECAUTIONS (cont'd)

- 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 concurrent use of XARELTO® and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of XARELTO®. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of XARELTO® is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. An indwelling epidural or intrathecal catheter should not be removed before at least 2 half-lives have elapsed (ie, 18 hours in young patients aged 20 to 45 years and 26 hours in elderly patients aged 60 to 76 years), after the last administration of XARELTO®. The next dose should not be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of XARELTO® for 24 hours. Monitor frequently to detect 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 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.

Please read additional Important Safety Information on the following pages and full [Prescribing Information](#) including **Boxed WARNINGS** for XARELTO®.



Clinical Trials

Safety Profile

Efficacy Profile

For treatment and
pediatric patients

Additional Adverse Events Summary

Other Adverse Reactions* Reported in XARELTO®-Treated Patients by ≥5% in EINSTEIN-Jr Study

Adverse Reaction	XARELTO® N=329 n (%)	Comparator Group N=162 n (%)
Pain in extremity	23 (7)	7 (4.3)
Fatigue†	23 (7)	7 (4.3)

*Adverse reaction with Relative Risk >1.5 for XARELTO® versus comparator.
†The following terms were combined: fatigue, asthenia.

A clinically relevant adverse reaction in XARELTO®-treated patients was vomiting (10.6% in the XARELTO® group vs 8% in the comparator group).

Close Window

[Additional Adverse Events Summary](#)

Not powered for noninferiority due to the low incidence of VTE in children and the lack of well-documented information on recurrence and treatment effect with standard anticoagulants in children; hence, there was no formal a priori sample size calculation.³

*Major bleeding is 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.

†Comparators were given at therapeutic doses, according to international guidelines, and included UFH, LMWH, or fondaparinux. Following completion of 5 to 9 days of standard anticoagulation, participants continued with heparin treatment or were switched to a VKA at the discretion of the treating physician for a main study treatment period of 3 months (or 1 month for children <2 years with CVC-VTE). A diagnostic imaging test was obtained at baseline and at the end of the main study treatment. When clinically necessary, treatment was extended up to 12 months in total (or up to 3 months in total for children <2 years with CVC-VTE).^{1,2,7}

‡Clinically relevant nonmajor bleeding is clinically overt bleeding, which did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact with a physician, temporary cessation of treatment, discomfort for the patient, or impairment of activities of daily life.

CVC-VTE = central venous catheter-related VTE; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist.

IMPORTANT SAFETY INFORMATION (cont'd) WARNINGS AND PRECAUTIONS (cont'd)

- 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 concurrent use of XARELTO® and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of XARELTO®. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of XARELTO® is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. An indwelling epidural or intrathecal catheter should not be removed before at least 2 half-lives have elapsed (ie, 18 hours in young patients aged 20 to 45 years and 26 hours in elderly patients aged 60 to 76 years), after the last administration of XARELTO®. The next dose should not be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of XARELTO® for 24 hours. Monitor frequently to detect 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 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.

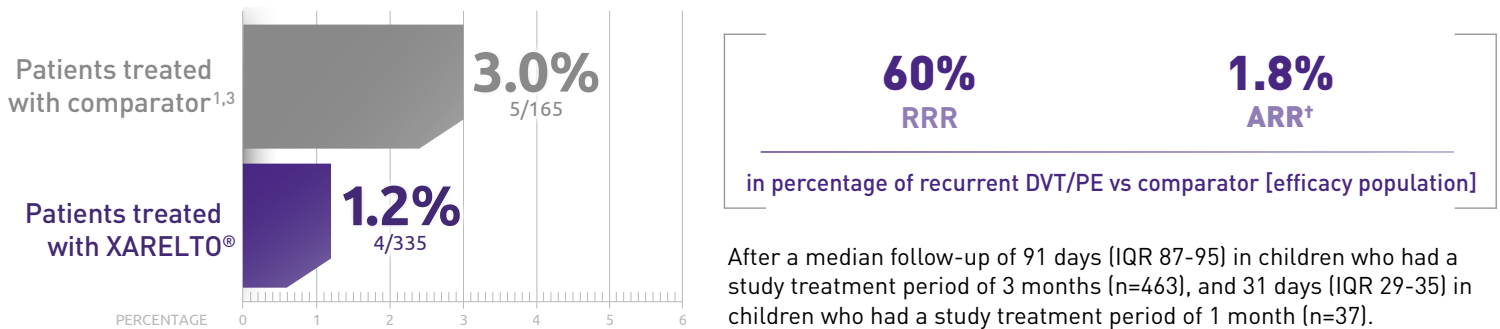
Please read additional Important Safety Information on the following pages and full [Prescribing Information](#) including **Boxed WARNINGS** for XARELTO®.

	Clinical Trials	Safety Profile	Efficacy Profile
For treatment and reduction of recurrence of VTE in pediatric patients from birth to <18 years of age	Dosing & Administration	Summary	

The EINSTEIN-Jr clinical trial was not powered for efficacy

60% RRR in recurrent VTE with XARELTO® vs standard anticoagulation^{3*}

Rates of recurrent DVT/PE (%) HR: 0.40; 95% CI: 0.11 to 1.41^{1,3}



Observed clot resolution over time: Complete resolution of index thrombus on repeat imaging

XARELTO®: 38% (128/335; 95% CI 33.0%, 43.5%) vs comparator: 26% (43/165; 95% CI 19.8%, 33.0%)^{1,3}

Symptomatic recurrent VTE or asymptomatic deterioration on repeat imaging

XARELTO®: 1.5% (5/335) vs comparator: 3.6% (6/165), (HR: 0.41; 95% CI 0.12 to 1.36)^{1,3}

Symptomatic recurrent VTE or major bleeding events

XARELTO®: 1.2% (4/335; 95% CI 0.4%, 3.0%) and comparator: 4.2% (7/165; 95% CI 2.0%, 8.4%)^{1,3}

Not powered for noninferiority due to the low incidence of VTE in children and the lack of well-documented information on recurrence and treatment effect with standard anticoagulants in children; hence, there was no formal a priori sample size calculation.³

*Comparators were given at therapeutic doses, according to international guidelines, and included UFH, LMWH, or fondaparinux. Following completion of 5 to 9 days of standard anticoagulation, participants continued with heparin treatment or were switched to a VKA at the discretion of the treating physician for a main study treatment period of 3 months (or 1 month for children <2 years with CVC-VTE). A diagnostic imaging test was obtained at baseline and at the end of the main study treatment. When clinically necessary, treatment was extended up to 12 months in total (or up to 3 months in total for children <2 years with CVC-VTE).^{1,3,7}

[†]ARR = 3.0-1.2 = 1.8.

ARR = absolute risk reduction; CI = confidence interval; CVC-VTE = central venous catheter-related VTE; HR = hazard ratio; IQR = interquartile range; LMWH = low-molecular-weight heparin;

OR = overall response; RRR = relative risk reduction; UFH = unfractionated heparin; VKA = vitamin K antagonist.

IMPORTANT SAFETY INFORMATION (cont'd) WARNINGS AND PRECAUTIONS (cont'd)

Use in Patients with Renal Impairment:

- **Nonvalvular Atrial Fibrillation:** Periodically assess renal function as clinically indicated (ie, more frequently in situations in which renal function may decline) and adjust therapy accordingly. Consider dose adjustment or discontinuation in patients who develop acute renal failure while on XARELTO®. Clinical efficacy and safety studies with XARELTO® did not enroll patients with CrCl <30 mL/min or end-stage renal disease (ESRD) on dialysis.
- **Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE:** In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO® in these patients. Discontinue XARELTO® in patients who develop acute renal failure while on treatment.

Please read additional Important Safety Information on the following pages and full [Prescribing Information](#) including **Boxed WARNINGS** for XARELTO®.



Clinical Trials

Safety Profile

Efficacy Profile

For treatment and reduction of recurrence of VTE in pediatric patients from birth to <18 years of age

Dosing & Administration

Summary

XARELTO® is the only FDA-approved antithrombotic treatment to offer pediatric patients both an oral suspension and tablets^{1,2}



oral suspension

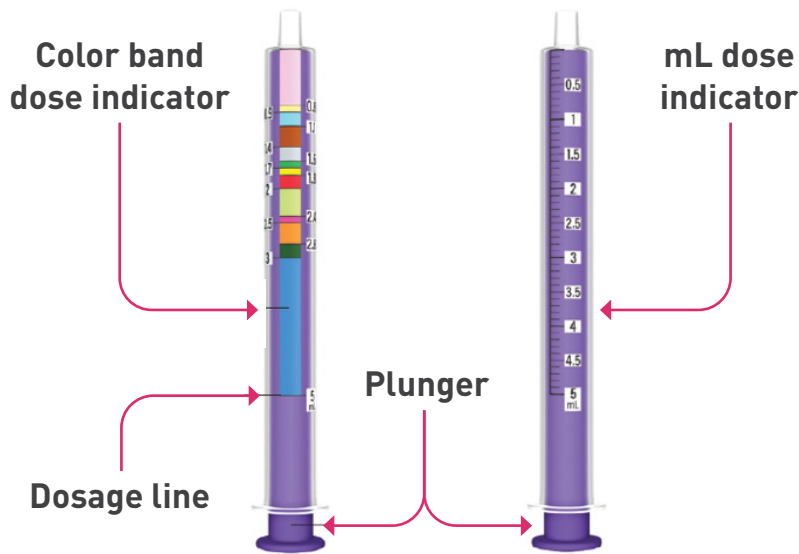


tablet

NO injections*

NO INR monitoring required

NO special diet required†



The oral-suspension formulation is administered through a color-coded device to help with dosing and administration

*After ≥5 days of parenteral treatment.

†All doses should be taken with feeding or with food since exposures match that of 20-mg daily dose in adults.

IMPORTANT SAFETY INFORMATION (cont'd) WARNINGS AND PRECAUTIONS (cont'd)

- Use in Patients with Renal Impairment (cont'd):**

- **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:** In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO® in these patients. Discontinue XARELTO® in patients who develop acute renal failure while on treatment.
- **Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding:** In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO® in these patients. Discontinue XARELTO® in patients who develop acute renal failure while on treatment.

Please read additional Important Safety Information on the following pages and full [Prescribing Information](#) including **Boxed WARNINGS** for XARELTO®.

For treatment and reduction of recurrence of VTE in pediatric patients from birth to <18 years of age

Pediatric dosing of XARELTO® is based on the child's weight¹

Recommended dosage in pediatric patients from birth to <18 years of age for treatment of VTE and reduction in risk of recurrent VTE**

DOSAGE FORM	BODY WEIGHT	1 mg XARELTO® = 1 mL SUSPENSION			
		DOSAGE			TOTAL DAILY DOSE†
		ONCE A DAY§	2 TIMES A DAY§	3 TIMES A DAY§	
Oral suspension only	2.6 to 2.9 kg			0.8 mg	2.4 mg
	3 to 3.9 kg			0.9 mg	2.7 mg
	4 to 4.9 kg			1.4 mg	4.2 mg
	5 to 6.9 kg			1.6 mg	4.8 mg
	7 to 7.9 kg			1.8 mg	5.4 mg
	8 to 8.9 kg			2.4 mg	7.2 mg
	9 to 9.9 kg			2.8 mg	8.4 mg
	10 to 11.9 kg			3 mg	9 mg
Oral suspension or tablets	12 to 29.9 kg		5 mg		10 mg
	30 to 49.9 kg	15 mg			15 mg
	≥50 kg	20 mg			20 mg

*Initiate XARELTO® treatment following ≥5 days of initial parenteral anticoagulation therapy.

†Patients <6 months of age should meet the following criteria: at birth were ≥37 weeks of gestation, have had ≥10 days of oral feeding, and weigh ≥2.6 kg at the time of dosing.

‡All doses should be taken with feeding or with food since exposures match that of 20-mg daily dose in adults.

§Once a day: approximately 24 hours apart; 2 times a day: approximately 12 hours apart; 3 times a day: approximately 8 hours apart.

Administration in pediatric patients¹

- Food Effect:**

For the treatment of VTE in children, the dose should be taken with food to increase absorption.

- Vomit or Spit up:**

If the patient vomits or spits up the dose within 30 minutes after receiving the dose, a new dose should be given. However, if the patient vomits >30 minutes after the dose is taken, the dose should not be readministered and the next dose should be taken as scheduled. If the patient vomits or spits up the dose repeatedly, the caregiver should contact the child's doctor right away.

- Tablets:**

- XARELTO® tablet must not be split in an attempt to provide a fraction of a tablet dose
- For children unable to swallow 10-mg, 15-mg, or 20-mg whole tablets, XARELTO® oral suspension should be used
- XARELTO® 2.5-mg tablets are not recommended for use in pediatric patients

- In Children <6 Months of Age:**

Dosing of XARELTO® was not studied and therefore dosing cannot be reliably determined in the following patient populations. Its use is therefore not recommended in children less than 6 months of age with any of the following:

- Less than 37 weeks of gestation at birth
- Less than 10 days of oral feeding
- Body weight of less than 2.6 kg

Monitor the child's weight and review the dose regularly, especially for children below 12 kg. This is to ensure a therapeutic dose is maintained.

Please see the "Instructions for Use" in [Prescribing Information](#) for directions on using the oral-suspension formulation.

IMPORTANT SAFETY INFORMATION (cont'd) WARNINGS AND PRECAUTIONS (cont'd)

- Use in Patients with Renal Impairment (cont'd):**

- **Reduction of Risk of Major Cardiovascular Events in Patients with CAD and Reduction of Risk of Major Thrombotic Vascular Events in Patients with PAD, Including Patients after Recent Lower Extremity Revascularization Due to Symptomatic PAD:** For patients with CrCl <15 mL/min, no data are available, and limited data are available for patients with a CrCl of 15 to 30 mL/min. In patients with CrCl <30 mL/min, a dose of 2.5 mg XARELTO® twice daily is expected to give an exposure similar to that in patients with moderate renal impairment (CrCl 30 to <50 mL/min), whose efficacy and safety outcomes were similar to those with preserved renal function. Clinical efficacy and safety studies with XARELTO® did not enroll patients with end-stage renal disease (ESRD) on dialysis.
- **Pediatric Patients:** There are limited clinical data in pediatric patients 1 year or older with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m²); therefore, avoid use of XARELTO® in these patients.

There are no clinical data in pediatric patients younger than 1 year with serum creatinine results above 97.5th percentile; therefore, avoid the use of XARELTO® in these patients.

Please read additional Important Safety Information on the following pages and full [Prescribing Information](#) including **Boxed WARNINGS** for XARELTO®.



Clinical Trials

Safety Profile

Efficacy Profile

For treatment and reduction of recurrence of VTE in pediatric patients from birth to <18 years of age

Dosing & Administration

Summary

Additional Administration Considerations

Use in renal impairment in pediatric patients:

PATIENTS 1 YEAR OF AGE OR OLDER:

- Mild renal impairment (eGFR: 50 to ≤ 80 mL/min/1.73 m²): no dose adjustment is required.
- Moderate or severe renal impairment (eGFR: <50 mL/min/1.73 m²): avoid use, as limited clinical data are available.
- eGFR can be done using the updated Schwartz formula, eGFR (Schwartz) = (0.413 x height in cm)/SCr in mg/dL, if SCr is measured by an enzymatic creatinine method that has been calibrated to be traceable to IDMS.
- If SCr is measured with routine methods that have not been recalibrated to be traceable to IDMS (eg, the traditional Jaffé reaction), the eGFR should be obtained from the original Schwartz formula: eGFR (mL/min/1.73 m²) = k * height (cm)/SCr (mg/dL), where k is proportionality constant:
 - k = 0.55 in children 1 year to 13 years
 - k = 0.55 in girls >13 and <18 years
 - k = 0.70 in boys >13 and <18 years

PATIENTS <1 YEAR OF AGE:

Determine renal function using serum creatinine. Avoid use of XARELTO® in pediatric patients younger than 1 year with serum creatinine results above 97.5th percentile, as no clinical data are available.

Reference values of serum creatinine in pediatric patients <1 year of age

Age	97.5 th percentile of creatinine (mg/dL)	97.5 th percentile of creatinine (µmol/L)
Week 2	0.52	46
Week 3	0.46	41
Week 4	0.42	37
Month 2	0.37	33
Month 3	0.34	30
Month 4-6	0.34	30
Month 7-9	0.34	30
Month 10-12	0.36	32

Pharmacokinetic Considerations:

- The half-life of rivaroxaban in plasma of pediatric patients treated for VTE decreased with decreasing age
- Mean half-life values were 4.2 hours in adolescents, 3 hours in children 2 to 12 years of age, 1.9 hours in children 0.5 to <2 years of age, and 1.6 hours in children <0.5 years of age
- An exploratory analysis in pediatric patients treated for VTE did not reveal relevant differences in rivaroxaban exposure based on gender

Switching to and from XARELTO®

From warfarin to XARELTO® - When switching patients from warfarin to XARELTO®, discontinue warfarin and start XARELTO® as soon as the INR is below 2.5 in pediatric patients to avoid periods of inadequate anticoagulation.

From XARELTO® to warfarin - To ensure adequate anticoagulation during the transition from XARELTO® to warfarin, continue XARELTO® for ≥ 2 days after the first dose of warfarin. After 2 days of coadministration, an INR should be obtained prior to the next scheduled dose of XARELTO®. Coadministration of XARELTO® and warfarin is advised to continue until the INR is ≥ 2.0 .

Once XARELTO® is discontinued, INR testing may be done reliably 24 hours after the last dose.

From XARELTO® to anticoagulants other than warfarin - For pediatric patients currently taking XARELTO® and transitioning to an anticoagulant with rapid onset, discontinue XARELTO® and give the first dose of the other anticoagulant (oral or parenteral) at the time that the next XARELTO® dose would have been taken.

From anticoagulants other than warfarin to XARELTO® - For pediatric patients currently receiving an anticoagulant other than warfarin, start XARELTO® 0 to 2 hours prior to the next scheduled administration of the drug (eg, LMWH or non-warfarin oral anticoagulant) and omit administration of the other anticoagulant. For UFH being administered by continuous infusion, stop the infusion and start XARELTO® at the same time.

Missed dose

- If XARELTO® is taken once a day, the patient should take the missed dose as soon as possible once it is noticed, but only on the same day. If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose
- If XARELTO® is taken 2 times a day, the patient should take the missed morning dose as soon as possible once it is noticed. A missed morning dose may be taken together with the evening dose. A missed evening dose can only be taken in the same evening
- If XARELTO® is taken 3 times a day, if a dose is missed, the patient should skip the missed dose and go back to the regular dosing schedule at the usual time without compensating for the missed dose

On the following day, the patient should continue with their regular regimen.

Administration options

Administration of XARELTO® suspension via NG tube or gastric feeding tube: XARELTO® oral suspension may be given through NG or gastric feeding tube. After the administration, flush the feeding tube with water.

For the treatment or reduction in risk of recurrent VTE in pediatric patients, the dose should then be immediately followed by enteral feeding to increase absorption.

An in vitro compatibility study indicated that XARELTO® oral suspension can be used with PVC, polyurethane or silicone NG tubing.

CHD = congenital heart disease; dL = deciliter; eGFR = estimated glomerular filtration rate; IDMS = isotope dilution mass spectrometry; INR = international normalized ratio; LMWH = low-molecular-weight heparin; µmol/L = micromole per liter; NG = nasogastric; PVC = polyvinyl chloride; UFH = unfractionated heparin.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Use in Patients with Hepatic Impairment:** No clinical data are available for adult patients with severe hepatic impairment. Avoid use 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. No clinical data are available in pediatric patients with hepatic impairment.
- **Use with P-gp and Strong CYP3A Inhibitors or Inducers:** Avoid concomitant use of XARELTO® with known combined P-gp and strong CYP3A inhibitors or inducers.

Please read additional Important Safety Information on the following pages and full [Prescribing Information](#) including **Boxed WARNINGS** for XARELTO®.



Clinical Trials

Safety Profile

Efficacy Profile

For treatment and reduction of recurrence of VTE in pediatric patients from birth to <18 years of age

Dosing & Administration

Summary

Pediatric VTE is complex.⁸ Helping protect against thrombosis doesn't have to be.

In EINSTEIN-Jr, the largest clinical trial in pediatric VTE treatment and first to evaluate a liquid formulation, XARELTO[®], compared with standard anticoagulation^{3-6*}:

The EINSTEIN-Jr clinical trial was not powered for efficacy

- **60% RRR, 1.8% ARR** in percentage of recurrent DVT/PE vs comparator
- **Similar rates of major and clinically relevant nonmajor bleeding** vs comparator

XARELTO[®] is the only FDA-APPROVED antithrombotic treatment to offer pediatric patients^{1,2}:



tablet



oral suspension

|| Not powered for noninferiority due to the low incidence of VTE in children and the lack of well-documented information on recurrence and treatment effect with standard anticoagulants in children; hence, there was no formal a priori sample size calculation.³

*Comparators were given at therapeutic doses, according to international guidelines, and included UFH, LMWH, or fondaparinux. Following completion of 5 to 9 days of standard anticoagulation, participants continued with heparin treatment or were switched to a VKA at the discretion of the treating physician for a main study treatment period of 3 months (or 1 month for children <2 years with CVC-VTE). A diagnostic imaging test was obtained at baseline and at the end of the main study treatment. When clinically necessary, treatment was extended up to 12 months in total (or up to 3 months in total for children <2 years with CVC-VTE).^{1,3,7}

CVC-VTE = central venous catheter-related VTE; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist.

IMPORTANT SAFETY INFORMATION (cont'd) WARNINGS AND PRECAUTIONS (cont'd)

- **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. Promptly evaluate signs or symptoms suggesting blood loss (eg, a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).
- **Patients with Prosthetic Heart Valves:** Use of XARELTO[®] is not recommended in patients who have had transcatheter aortic valve replacement (TAVR), based on the results of the GALILEO study, which reported higher rates of death and bleeding in patients randomized to XARELTO[®] compared to those randomized to an antiplatelet regimen. Safety and efficacy of XARELTO[®] have not been studied in patients with other prosthetic heart valves or other valve procedures. Use of XARELTO[®] is not recommended in patients with prosthetic heart valves.
- **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.

Please read additional Important Safety Information on the following pages and full [Prescribing Information](#) including **Boxed WARNINGS** for XARELTO[®].

References: 1. XARELTO[®] [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2. Pradaxa[®] [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2021. 3. Male C, Lensing AWA, Palumbo JS, et al; EINSTEIN-Jr Phase 3 Investigators. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. *Lancet Haematol.* 2019;7(1):e18-e27. 4. ClinicalTrials.gov. NCT01895777. Open label study comparing efficacy and safety of dabigatran etexilate to standard of care in paediatric patients with venous thromboembolism (VTE). Accessed November 3, 2021. 5. ClinicalTrials.gov. NCT02464969. Apixaban for the acute treatment of venous thromboembolism in children. Accessed November 3, 2021. 6. ClinicalTrials.gov. NCT02798471. Hokusai study in pediatric patients with confirmed venous thromboembolism (VTE). Accessed November 3, 2021. 7. Lensing AWA, Male C, Young G, et al. Rivaroxaban versus standard anticoagulation for acute venous thromboembolism in childhood. Design of the EINSTEIN-Jr phase III study. *Thromb J.* 2018;16:34. doi:10.1186/s12959-018-0188-y 8. Monagle P, Cuello CA, Augustine C, et al. American Society of Hematology 2018 Guidelines for Management of Venous Thromboembolism: treatment of pediatric venous thromboembolism. *Blood Adv.* 2018;2(22):3292-3316. DOI: 10.1182/bloodadvances.2018024828



Clinical Trials

Safety Profile

Efficacy Profile

For thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure

Dosing & Administration

Summary



Evaluated in the UNIVERSE clinical trial

XARELTO[®] is the only anticoagulant FDA approved for use in children with congenital heart disease as thromboprophylaxis post-Fontan procedure^{1,2}

XARELTO[®] is indicated for thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure.

[View Clinical Trial](#)

IMPORTANT SAFETY INFORMATION (cont'd) WARNINGS AND PRECAUTIONS (cont'd)

- **Increased Risk of Thrombosis in Patients with Antiphospholipid Syndrome:** Direct-acting oral anticoagulants (DOACs), including XARELTO[®], are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

DRUG INTERACTIONS

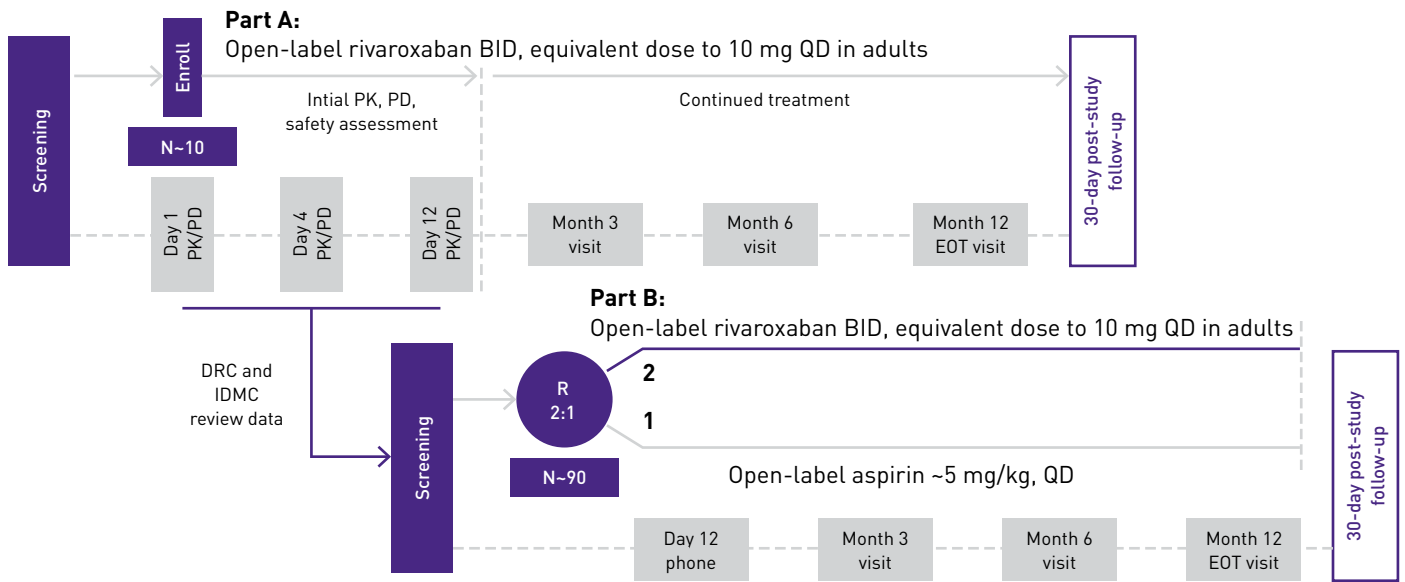
- Combined P-gp and strong CYP3A inhibitors increase exposure to rivaroxaban and may increase risk of bleeding.
- Combined P-gp and strong CYP3A inducers decrease exposure to rivaroxaban and may increase risk of thromboembolic events.
- XARELTO[®] should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A inhibitors (eg, erythromycin) unless the potential benefit justifies the potential risk.
- Coadministration of enoxaparin, warfarin, aspirin, clopidogrel, and chronic NSAID use may increase risk of bleeding.
- Avoid concurrent use of XARELTO[®] with other anticoagulants due to increased bleeding risk, unless benefit outweighs risk. Promptly evaluate signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs.

Please read additional Important Safety Information on the following pages and full [Prescribing Information](#) including **Boxed WARNINGS** for XARELTO[®].

In the UNIVERSE clinical trial

The first and only randomized study of a direct oral anticoagulant (DOAC) conducted to evaluate thromboprophylaxis in children post Fontan³

Objective | Randomized, multicenter, open-label, active-controlled, 2-part, phase 3 study to examine the use of a novel, oral suspension formulation of XARELTO® in children 2-8 years old with single ventricle physiology who had the Fontan procedure within 4 months before enrollment^{2,3}



The UNIVERSE clinical trial comprised 2 parts²:

- Part A assessed the PK and PD of XARELTO® in young children to determine a dose that would approximate the drug exposure achieved in adults with XARELTO® 10 mg QD
- Part B evaluated the safety and efficacy of XARELTO® vs aspirin for thromboprophylaxis post-Fontan procedure for 12 months

Not powered to test formal hypotheses for efficacy and safety due to the limited availability of the study population and the expected low event rates.^{2,3}

BID = twice daily; DRC = Data Review Committee; EOT = end of treatment; IDMC = independent data monitoring committee; PD = pharmacodynamics; PK = pharmacokinetics; QD = every day; R = randomization.

IMPORTANT SAFETY INFORMATION (cont'd) USE IN SPECIFIC POPULATIONS

- **Pregnancy:** The limited available data on XARELTO® in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Use XARELTO® with caution in pregnant patients because of the potential for pregnancy-related hemorrhage and/or emergent delivery. The anticoagulant effect of XARELTO® cannot be reliably monitored with standard laboratory testing. Consider the benefits and risks of XARELTO® for the mother and possible risks to the fetus when prescribing to a pregnant woman.
 - **Fetal/Neonatal adverse reactions:** Based on the pharmacologic activity of Factor Xa inhibitors and the potential to cross the placenta, bleeding may occur at any site in the fetus and/or neonate.

Please read additional Important Safety Information on the following pages and full [Prescribing Information](#) including **Boxed WARNINGS** for XARELTO®.

**Clinical Trial****Safety Profile****Efficacy Profile**

For thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure

Dosing & Administration**Summary**

UNIVERSE clinical trial study design^{2,3}

STUDY POPULATION

- Children aged 2-8 years with single ventricle physiology, post-Fontan procedure (within 4 months prior to study enrollment)
- This was a VTE-prevention study; patients with thrombosis requiring treatment were excluded
- Main exclusion criteria:
 - Evidence of thrombosis
 - History of GI disease or surgery associated with impaired absorption
 - Active bleeding or high risk of bleeding contraindicating antiplatelet or anticoagulation therapy, including history of intracranial hemorrhage, or contraindication to aspirin or rivaroxaban
 - Chronic use of NSAIDs
 - Platelet count $<50 \times 10^9/L$ at screening
 - Estimated eGFR $<30 \text{ mL/min/1.73m}^2$

TREATMENT GROUPS

- Subjects were randomized (2:1) to XARELTO[®] or antiplatelet therapy with aspirin (N=112)
- XARELTO[®] was administered BID as a suspension; weight-adjusted to achieve drug exposure comparable to the thromboprophylactic 10 mg/day dose in adults
- Aspirin dose: 5 mg/kg/day, up to a maximum of 81 to 100 mg/day (per local practice)

OUTCOMES

- **Primary efficacy outcome:** Any thrombotic event, venous or arterial
- **Safety outcomes:** Major bleeding events (primary); nonmajor and trivial/minimal bleeding (secondary)

|| Not powered to test formal hypotheses for efficacy and safety due to the limited availability of the study population and the expected low event rates.^{2,3}

BID = twice a day; eGFR = glomerular filtration rate; NSAIDs = nonsteroidal anti-inflammatory drugs.

IMPORTANT SAFETY INFORMATION (cont'd) USE IN SPECIFIC POPULATIONS (cont'd)

- **Pregnancy (cont'd):**
 - **Labor or delivery:** The risk of bleeding should be balanced with the risk of thrombotic events when considering use in this setting.
 - There are no adequate or well-controlled studies of XARELTO[®] in pregnant women, and dosing for pregnant women has not been established. Post-marketing experience is currently insufficient to determine a rivaroxaban-associated risk for major birth defects or miscarriage.
- **Lactation:** Rivaroxaban has been detected in human milk. There are insufficient data to determine the effects of rivaroxaban on the breastfed child or on milk production. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for XARELTO[®] and any potential adverse effects on the breastfed infant from XARELTO[®] or from the underlying maternal condition.
- **Females and Males of Reproductive Potential:** Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician. The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants, including XARELTO[®], should be assessed in females of reproductive potential and those with abnormal uterine bleeding.

Please read additional Important Safety Information on the following pages and full [Prescribing Information](#) including **Boxed WARNINGS** for XARELTO[®].



Clinical Trials

Safety Profile

Efficacy Profile

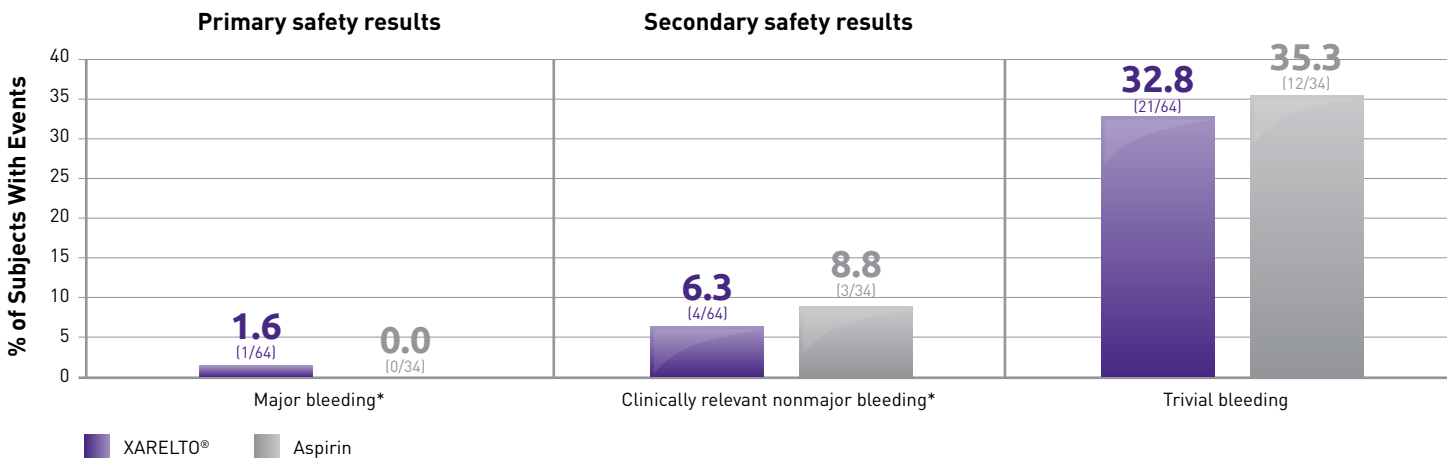
For thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure

Dosing & Administration

Summary

In the UNIVERSE clinical trial

A comparable prevalence of overall bleeding events was observed with XARELTO® versus aspirin¹



Bleeding events were comparable across treatment groups^{1,2*}

Major Bleed: single case of epistaxis (nose bleed) occurred in the rivaroxaban part B group.

Trivial bleeds: most frequent site of trivial bleeding was the skin in both groups.

Clinically relevant nonmajor bleeds: with rivaroxaban, bleeding events occurred in the lower GI tract, gingival tissue, and skin; with ASA, these events occurred in the lower GI tract, skin, hematoma, and subconjunctival tissue.

Not powered to test formal hypotheses for efficacy and safety due to the limited availability of the study population and the expected low event rates.^{2,3}

[Additional Adverse Events Summary](#) ↗

*Clinically relevant nonmajor bleeding is clinically overt bleeding, which did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact with a physician, temporary cessation of treatment, discomfort for the patient, or impairment of activities of daily life. Major bleeding is 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.

ASA = aspirin; GI = gastrointestinal.

IMPORTANT SAFETY INFORMATION (cont'd) USE IN SPECIFIC POPULATIONS (cont'd)

- Pediatric Use:** XARELTO® was not studied and therefore dosing cannot be reliably determined or recommended in children less than 6 months who were less than 37 weeks of gestation at birth, had less than 10 days of oral feeding, or had a body weight of less than 2.6 kg.

Clinical studies that evaluated safety, efficacy, and pharmacokinetic/pharmacodynamic data support the use of XARELTO® 10-mg, 15-mg, and 20-mg tablets in pediatric patients. For the XARELTO® 2.5-mg tablets, there are no safety, efficacy, and

Please read additional Important Safety Information on the following pages and full [Prescribing Information](#) including **Boxed WARNINGS** for XARELTO®.



Clinical Trials

Safety

Efficacy Profile

For thromboprophylaxis in
congenital heart disease

Summary of Adverse Events in UNIVERSE²

Other Adverse Reactions* Reported by ≥5% of XARELTO[®]-Treated Patients in UNIVERSE Study (Part B)

Adverse Reaction	XARELTO [®] N=64 n (%)	Comparator Group N=34 n (%)
Cough	10 (15.6)	3 (8.8)
Vomiting	9 (14.1)	3 (8.8)
Gastroenteritis [†]	8 (12.5)	1 (2.9)
Rash [†]	6 (9.4)	2 (5.9)

*Adverse reaction with Relative Risk >1.5 for XARELTO[®] versus aspirin.

[†]The following terms were combined:
Gastroenteritis: gastroenteritis, gastroenteritis viral
Rash: rash, rash maculo-papular, viral rash

← Close Window

% of Subjects With Events



Major bleeding*

Clinically relevant nonmajor bleeding*

Trivial bleeding

XARELTO[®]

Aspirin

Bleeding events were comparable across treatment groups^{1,2*}

Major Bleed: single case of epistaxis (nose bleed) occurred in the rivaroxaban part B group.

Trivial bleeds: most frequent site of trivial bleeding was the skin in both groups.

Clinically relevant nonmajor bleeds: with rivaroxaban, bleeding events occurred in the lower GI tract, gingival tissue, and skin; with ASA, these events occurred in the lower GI tract, skin, hematoma, and subconjunctival tissue.

Not powered to test formal hypotheses for efficacy and safety due to the limited availability of the study population and the expected low event rates.^{2,3}

[Additional Adverse Events Summary](#) →

*Clinically relevant nonmajor bleeding is clinically overt bleeding, which did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact with a physician, temporary cessation of treatment, discomfort for the patient, or impairment of activities of daily life. Major bleeding is 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.

ASA = aspirin; GI = gastrointestinal.

IMPORTANT SAFETY INFORMATION (cont'd) USE IN SPECIFIC POPULATIONS (cont'd)

• **Pediatric Use:** XARELTO[®] was not studied and therefore dosing cannot be reliably determined or recommended in children less than 6 months who were less than 37 weeks of gestation at birth, had less than 10 days of oral feeding, or had a body weight of less than 2.6 kg.

Clinical studies that evaluated safety, efficacy, and pharmacokinetic/pharmacodynamic data support the use of XARELTO[®] 10-mg, 15-mg, and 20-mg tablets in pediatric patients. For the XARELTO[®] 2.5-mg tablets, there are no safety, efficacy, and

Please read additional Important Safety Information on the following page and full [Prescribing Information](#) including **Boxed WARNINGS** for XARELTO[®].



Clinical Trials

Safety Profile

Efficacy Profile

For thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure

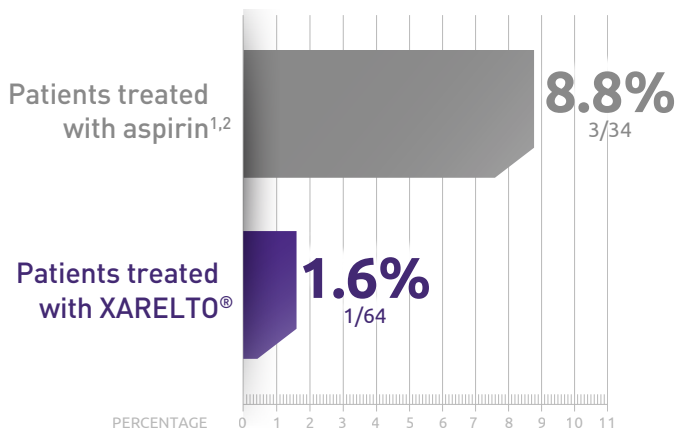
Dosing & Administration

Summary

The UNIVERSE clinical trial was not powered for statistical significance

XARELTO[®] was evaluated for the prevention of thrombotic events in pediatric patients post Fontan²

Rates of thrombotic events (%)



Efficacy outcomes^{1,2*}

Event	Treatment Arm [†]	
	XARELTO ^{®‡} N=64 [%]	Aspirin [‡] N=34 [%]
Primary efficacy outcome	1 (1.6%)	3 (8.8%)
Ischemic stroke	0	1 (2.9%)
Pulmonary embolism	1 (1.6%)	0
Venous thrombosis	0	2 (5.9%)

Not powered to test formal hypotheses for efficacy and safety due to the limited availability of the study population and the expected low event rates.^{2,3}

*Efficacy outcomes based on full analysis set: all participants in part A who received ≥ 1 dose of study drug and all participants in part B who were randomized and received ≥ 1 dose of study drug. In the rivaroxaban part A group, 1 participant (8%) had a venous thrombotic event on day 362 of treatment (364 days post Fontan procedure). This study was not powered for efficacy hypothesis testing (post hoc log-rank test $P=0.095$).²

[†]Part B: randomized 2:1 (XARELTO[®]: aspirin).

[‡]Treatment schedule: body weight-adjusted doses of XARELTO[®] (exposures to match that of 10 mg QD in adults) or aspirin (approximately 5 mg/kg).

QD = every day.

IMPORTANT SAFETY INFORMATION (cont'd) USE IN SPECIFIC POPULATIONS (cont'd)

- Pediatric Use (con'td):** pharmacokinetic/pharmacodynamic data to support the use in pediatric patients. Therefore, XARELTO[®] 2.5-mg tablets are not recommended for use in pediatric patients.

Although not all adverse reactions identified in the adult population have been observed in clinical trials of children and adolescent patients, the same warnings and precautions for adults should be considered for children and adolescents.

- Geriatric Use:** 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.

Please read additional Important Safety Information on the following page and full [Prescribing Information](#) including **Boxed WARNINGS** for XARELTO[®].



Clinical Trials

Safety Profile

Efficacy Profile

For thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure

Dosing & Administration

Summary

XARELTO[®] is the only FDA-approved antithrombotic treatment to offer pediatric patients both an oral suspension and tablets^{1,4}



oral suspension

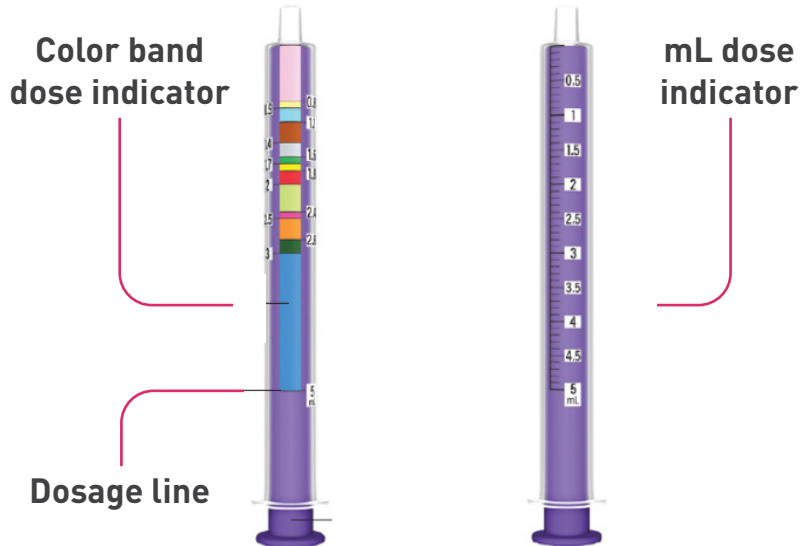


tablet

NO injections

NO INR monitoring required

NO special diet required*



The oral-suspension formulation is administered through a color-coded device to help with dosing and administration

*All doses can be taken with or without food since exposures match that of 10-mg daily dose in adults.

IMPORTANT SAFETY INFORMATION (cont'd) OVERDOSAGE

- Overdose of XARELTO[®] may lead to hemorrhage. Discontinue XARELTO[®] and initiate appropriate therapy if bleeding complications associated with overdosage occur. An agent to reverse the anti-factor Xa activity of rivaroxaban is available.

ADVERSE REACTIONS

- Most common adverse reactions in adult patients with XARELTO[®] were bleeding complications.
- Most common adverse reactions in pediatric patients were bleeding, cough, vomiting, and gastroenteritis.

Please read full [Prescribing Information](#), including **Boxed WARNINGS** for XARELTO[®].

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Clinical Trials

Safety Profile

Efficacy Profile

For thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure

Dosing & Administration

Summary

Pediatric dosing of XARELTO® is based on the child's weight¹

Recommended dosage for thromboprophylaxis in pediatric patients with CHD after the Fontan procedure.

DOSAGE FORM	BODY WEIGHT	1 mg XARELTO® = 1 mL SUSPENSION		
		DOSAGE		TOTAL DAILY DOSE*
		ONCE A DAY†	2 TIMES A DAY†	
Oral suspension only	7 to 7.9 kg		1.1 mg	2.2 mg
	8 to 9.9 kg		1.6 mg	3.2 mg
	10 to 11.9 kg		1.7 mg	3.4 mg
	12 to 19.9 kg		2 mg	4 mg
	20 to 29.9 kg		2.5 mg	5 mg
	30 to 49.9 kg	7.5 mg		7.5 mg
Oral suspension or tablets	≥50 kg	10 mg		10 mg

Administration in pediatric patients¹

- **Food Effect:**
For thromboprophylaxis after Fontan procedure, the dose can be taken with or without food.
- **Vomit or Spit up:**
If the patient vomits or spits up the dose within 30 minutes after receiving the dose, a new dose should be given. However, if the patient vomits more than 30 minutes after the dose is taken, the dose should not be readministered and the next dose should be taken as scheduled. If the patient vomits or spits up the dose repeatedly, the caregiver should contact the child's doctor right away.
- **Tablets:**
 - XARELTO® tablet must not be split in an attempt to provide a fraction of a tablet dose
 - For children unable to swallow 10-mg, 15-mg, or 20-mg whole tablets, XARELTO® oral suspension should be used.
 - XARELTO® 2.5-mg tablets are not recommended for use in pediatric patients
- Monitor the child's weight and review the dose regularly, especially for children below 12 kg. This is to ensure a therapeutic dose is maintained.

Please see the "Instructions for Use" in [Prescribing Information](#) for directions on using the oral-suspension formulation.

*All doses can be taken with or without food.

†Once a day: approximately 24 hours apart; 2 times a day: approximately 12 hours apart.

CHD = congenital heart disease.

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

Please read additional Important Safety Information on the following pages and full [Prescribing Information](#) including **Boxed WARNINGS** for XARELTO®.



Clinical Trials

Safety Profile

Efficacy Profile

For thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure

Dosing & Administration

Summary

Additional Administration Considerations

Use in renal impairment in pediatric patients:

PATIENTS 1 YEAR OF AGE OR OLDER:

- Mild renal impairment (eGFR: 50 to ≤ 80 mL/min/1.73 m²): no dose adjustment is required.
- Moderate or severe renal impairment (eGFR: < 50 mL/min/1.73 m²): avoid use, as limited clinical data are available
- eGFR can be done using the updated Schwartz formula, eGFR (Schwartz) = $(0.413 \times \text{height in cm}) / \text{SCr in mg/dL}$, if SCr is measured by an enzymatic creatinine method that has been calibrated to be traceable to IDMS.
- If SCr is measured with routine methods that have not been recalibrated to be traceable to IDMS (eg, the traditional Jaffé reaction), the eGFR should be obtained from the original Schwartz formula: eGFR (mL/min/1.73 m²) = $k \times \text{height (cm)} / \text{SCr (mg/dL)}$, where k is proportionality constant:
 - k = 0.55 in children 1 year to 13 years
 - k = 0.55 in girls > 13 and < 18 years
 - k = 0.70 in boys > 13 and < 18 years

PATIENTS < 1 YEAR OF AGE:

Determine renal function using serum creatinine. Avoid use of XARELTO® in pediatric patients younger than 1 year with serum creatinine results above 97.5th percentile, as no clinical data are available.

Reference values of serum creatinine in pediatric patients < 1 year of age

Age	97.5 th percentile of creatinine (mg/dL)	97.5 th percentile of creatinine (μmol/L)
Week 2	0.52	46
Week 3	0.46	41
Week 4	0.42	37
Month 2	0.37	33
Month 3	0.34	30
Month 4-6	0.34	30
Month 7-9	0.34	30
Month 10-12	0.36	32

Pharmacokinetic Considerations:

- The half-life of rivaroxaban in plasma of pediatric patients treated for VTE decreased with decreasing age
- Mean half-life values were 4.2 hours in adolescents, 3 hours in children 2 to 12 years of age, 1.9 hours in children 0.5 to < 2 years of age, and 1.6 hours in children < 0.5 years of age
- An exploratory analysis in pediatric patients treated for VTE did not reveal relevant differences in rivaroxaban exposure based on gender

Switching to and from XARELTO®

From warfarin to XARELTO® - When switching patients from warfarin to XARELTO®, discontinue warfarin and start XARELTO® as soon as the INR is below 2.5 in pediatric patients to avoid periods of inadequate anticoagulation.

From XARELTO® to warfarin - To ensure adequate anticoagulation during the transition from XARELTO® to warfarin, continue XARELTO® for ≥ 2 days after the first dose of warfarin. After 2 days of coadministration, an INR should be obtained prior to the next scheduled dose of XARELTO®. Coadministration of XARELTO® and warfarin is advised to continue until the INR is ≥ 2.0 .

Once XARELTO® is discontinued, INR testing may be done reliably 24 hours after the last dose.

From XARELTO® to anticoagulants other than warfarin - For pediatric patients currently taking XARELTO® and transitioning to an anticoagulant with rapid onset, discontinue XARELTO® and give the first dose of the other anticoagulant (oral or parenteral) at the time that the next XARELTO® dose would have been taken.

From anticoagulants other than warfarin to XARELTO® - For pediatric patients currently receiving an anticoagulant other than warfarin, start XARELTO® 0 to 2 hours prior to the next scheduled administration of the drug (eg, LMWH or non-warfarin oral anticoagulant) and omit administration of the other anticoagulant. For UFH being administered by continuous infusion, stop the infusion and start XARELTO® at the same time.

Missed dose

- If XARELTO® is taken once a day, the patient should take the missed dose as soon as possible once it is noticed, but only on the same day. If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose
- If XARELTO® is taken 2 times a day, the patient should take the missed morning dose as soon as possible once it is noticed. A missed morning dose may be taken together with the evening dose. A missed evening dose can only be taken in the same evening

On the following day, the patient should continue with their regular regimen.

Administration options

Administration of XARELTO® suspension via NG tube or gastric feeding tube: XARELTO® oral suspension may be given through NG or gastric feeding tube. After the administration, flush the feeding tube with water.

For thromboprophylaxis in pediatric patients with CHD who have undergone the Fontan procedure, the dose is not required to be followed by enteral feeding.

An in vitro compatibility study indicated that XARELTO® oral suspension can be used with PVC, polyurethane or silicone NG tubing.

CHD = congenital heart disease; dL = deciliter; eGFR = estimated glomerular filtration rate; IDMS = isotope dilution mass spectrometry; INR = international normalized ratio; LMWH = low-molecular-weight heparin; μmol/L = micromole per liter; NG = nasogastric; PVC = polyvinyl chloride; UFH = unfractionated heparin.

IMPORTANT SAFETY INFORMATION (cont'd)

- **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.



Clinical Trials

Safety Profile

Efficacy Profile

For thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure

Dosing & Administration

Summary

Pediatric post-Fontan care is complex.⁵ Helping protect against thrombosis doesn't have to be.

In the UNIVERSE study², the first and only randomized study of a DOAC to prevent thromboembolism in children post Fontan procedure, XARELTO[®] versus aspirin:

The UNIVERSE clinical trial was not powered for statistical significance

- Numerically fewer thrombotic events vs aspirin
- Similar safety profile vs aspirin was observed

XARELTO[®] is the only FDA-APPROVED antithrombotic treatment to offer pediatric patients^{1,4}:



tablet



oral suspension

Not powered to test formal hypotheses for efficacy and safety due to the limited availability of the study population and the expected low event rates.^{2,3}

DOAC = direct oral anticoagulant.

IMPORTANT SAFETY INFORMATION (cont'd)

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to XARELTO[®] (eg, anaphylactic 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.

Please read additional Important Safety Information on the following pages and full [Prescribing Information](#) including **Boxed WARNINGS** for XARELTO[®].

References: 1. XARELTO[®] [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2. McCrindle BW, Michelson AD, Van Bergen AH, et al; UNIVERSE Study Investigators. Thromboprophylaxis for children post-Fontan procedure: insights from the UNIVERSE study. *J Am Heart Assoc.* 2021;e021765. doi:10.1161/JAHA.120.021765 3. Pina LM, Dong X, Zhang L, et al. Rivaroxaban, a direct Factor Xa inhibitor, versus acetylsalicylic acid as thromboprophylaxis in children post-Fontan procedure: rationale and design of a prospective, randomized trial [the UNIVERSE study]. *Am Heart J.* 2019;213:97-104. doi:10.1016/j.ahj.2019.04.009 4. Pradaxa[®] [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2021 5. Giglia TM, Massicotte MP, Tweddell JS, et al. Prevention and treatment of thrombosis in pediatric and congenital heart disease. A scientific statement from the American Heart Association. *Circulation.* 2013;128(24):2622-2703. DOI: 10.1161/01.cir.0000436140.77832.7a

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **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 in patients with active pathological hemorrhage.
 - An agent to reverse the anti-factor Xa activity of rivaroxaban is available. Because of high plasma protein binding, rivaroxaban is not dialyzable.
 - Concomitant use of other drugs that impair hemostasis increases risk of bleeding. These include aspirin, P2Y₁₂ platelet inhibitors, dual antiplatelet therapy, other antithrombotic agents, fibrinolytic therapy, NSAIDs, selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs).
 - Risk of Hemorrhage in Acutely Ill Medical Patients at High Risk of Bleeding: Acutely ill medical patients with the following conditions are at increased risk of bleeding with the use of XARELTO® for primary VTE prophylaxis: history of bronchiectasis, pulmonary cavitation, or pulmonary hemorrhage; active cancer (ie, undergoing acute, in-hospital cancer treatment); active gastroduodenal ulcer or history of bleeding in the three months prior to treatment; or dual antiplatelet therapy. XARELTO® is not for use for primary VTE prophylaxis in these hospitalized, acutely ill medical patients at high risk of bleeding.
- **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 concurrent use of XARELTO® and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of XARELTO®. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of XARELTO® is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. An indwelling epidural or intrathecal catheter should not be removed before at least 2 half-lives have elapsed (ie, 18 hours in young patients aged 20 to 45 years and 26 hours in elderly patients aged 60 to 76 years), after the last administration of XARELTO®. The next dose should not be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of XARELTO® for 24 hours. Monitor frequently to detect 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 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:** Periodically assess renal function as clinically indicated (ie, more frequently in situations in which renal function may decline) and adjust therapy accordingly. Consider dose adjustment or discontinuation in patients who develop acute renal failure while on XARELTO®. Clinical efficacy and safety studies with XARELTO® did not enroll patients with CrCl <30 mL/min or end-stage renal disease (ESRD) on dialysis.
 - **Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE:** In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO® in these patients. Discontinue XARELTO® in patients who develop acute renal failure while on treatment.
 - **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:** In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO® in these patients. Discontinue XARELTO® in patients who develop acute renal failure while on treatment.
 - **Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding:** In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min; therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl <15 mL/min (including patients on dialysis); therefore, avoid the use of XARELTO® in these patients. Discontinue XARELTO® in patients who develop acute renal failure while on treatment.

Please read additional Important Safety Information on the following pages and full [Prescribing Information](#) including Boxed WARNINGS for XARELTO®.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Use in Patients with Renal Impairment (cont'd):**

- **Reduction of Risk of Major Cardiovascular Events in Patients with CAD and Reduction of Risk of Major Thrombotic Vascular Events in Patients with PAD, Including Patients after Recent Lower Extremity Revascularization Due to Symptomatic PAD:**

For patients with CrCl <15 mL/min, no data are available, and limited data are available for patients with a CrCl of 15 to 30 mL/min. In patients with CrCl <30 mL/min, a dose of 2.5 mg XARELTO® twice daily is expected to give an exposure similar to that in patients with moderate renal impairment (CrCl 30 to <50 mL/min), whose efficacy and safety outcomes were similar to those with preserved renal function. Clinical efficacy and safety studies with XARELTO® did not enroll patients with end-stage renal disease (ESRD) on dialysis.

- **Pediatric Patients:** There are limited clinical data in pediatric patients 1 year or older with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m²); therefore, avoid use of XARELTO® in these patients.

There are no clinical data in pediatric patients younger than 1 year with serum creatinine results above 97.5th percentile; therefore, avoid the use of XARELTO® in these patients.

- **Use in Patients with Hepatic Impairment:** No clinical data are available for adult patients with severe hepatic impairment. Avoid use 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. No clinical data are available in pediatric patients with hepatic impairment.

- **Use with P-gp and Strong CYP3A Inhibitors or Inducers:** Avoid concomitant use of XARELTO® with known combined P-gp and strong CYP3A inhibitors or inducers.

- **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. Promptly evaluate signs or symptoms suggesting blood loss (eg, a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).

- **Patients with Prosthetic Heart Valves:** Use of XARELTO® is not recommended in patients who have had transcatheter aortic valve replacement (TAVR), based on the results of the GALILEO study, which reported higher rates of death and bleeding in patients randomized to XARELTO® compared to those randomized to an antiplatelet regimen. Safety and efficacy of XARELTO®

have not been studied in patients with other prosthetic heart valves or other valve procedures. Use of XARELTO® is not recommended in patients with prosthetic heart valves.

- **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.

- **Increased Risk of Thrombosis in Patients with Antiphospholipid Syndrome:** Direct-acting oral anticoagulants (DOACs), including XARELTO®, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

DRUG INTERACTIONS

- Combined P-gp and strong CYP3A inhibitors increase exposure to rivaroxaban and may increase risk of bleeding.
- Combined P-gp and strong CYP3A inducers decrease exposure to rivaroxaban and may increase risk of thromboembolic events.
- XARELTO® should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A inhibitors (eg, erythromycin) unless the potential benefit justifies the potential risk.
- Coadministration of enoxaparin, warfarin, aspirin, clopidogrel, and chronic NSAID use may increase risk of bleeding.
- Avoid concurrent use of XARELTO® with other anticoagulants due to increased bleeding risk, unless benefit outweighs risk. Promptly evaluate signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs.

Please read additional Important Safety Information on the following page and full [Prescribing Information](#) including Boxed WARNINGS for XARELTO®.

IMPORTANT SAFETY INFORMATION (cont'd)

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** The limited available data on XARELTO® in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Use XARELTO® with caution in pregnant patients because of the potential for pregnancy-related hemorrhage and/or emergent delivery. The anticoagulant effect of XARELTO® cannot be reliably monitored with standard laboratory testing. Consider the benefits and risks of XARELTO® for the mother and possible risks to the fetus when prescribing to a pregnant woman.
 - **Fetal/Neonatal adverse reactions:** Based on the pharmacologic activity of Factor Xa inhibitors and the potential to cross the placenta, bleeding may occur at any site in the fetus and/or neonate.
 - **Labor or delivery:** The risk of bleeding should be balanced with the risk of thrombotic events when considering use in this setting.
 - There are no adequate or well-controlled studies of XARELTO® in pregnant women, and dosing for pregnant women has not been established. Post-marketing experience is currently insufficient to determine a rivaroxaban-associated risk for major birth defects or miscarriage.
- **Lactation:** Rivaroxaban has been detected in human milk. There are insufficient data to determine the effects of rivaroxaban on the breastfed child or on milk production. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for XARELTO® and any potential adverse effects on the breastfed infant from XARELTO® or from the underlying maternal condition.
- **Females and Males of Reproductive Potential:** Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician. The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants, including XARELTO®, should be assessed in females of reproductive potential and those with abnormal uterine bleeding.
- **Pediatric Use:** XARELTO® was not studied and therefore dosing cannot be reliably determined or recommended in children less than 6 months who were less than 37 weeks of gestation at birth, had less than 10 days of oral feeding, or had a body weight of less than 2.6 kg.

Clinical studies that evaluated safety, efficacy, and pharmacokinetic/pharmacodynamic data support the use of XARELTO® 10-mg, 15-mg, and 20-mg tablets in pediatric patients. For the XARELTO® 2.5-mg tablets, there are no safety, efficacy, and pharmacokinetic/pharmacodynamic data to support the use in pediatric patients. Therefore, XARELTO® 2.5-mg tablets are not recommended for use in pediatric patients.

Although not all adverse reactions identified in the adult population have been observed in clinical trials of children and adolescent patients, the same warnings and precautions for adults should be considered for children and adolescents.

- **Geriatric Use:** 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.

OVERDOSAGE

- Overdose of XARELTO® may lead to hemorrhage. Discontinue XARELTO® and initiate appropriate therapy if bleeding complications associated with overdosage occur. An agent to reverse the anti-factor Xa activity of rivaroxaban is available.

ADVERSE REACTIONS

- Most common adverse reactions in adult patients with XARELTO® were bleeding complications.
- Most common adverse reactions in pediatric patients were bleeding, cough, vomiting, and gastroenteritis.

Please read full [Prescribing Information](#), including **Boxed WARNINGS** for XARELTO®.

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Questions? Call JanssenMD®.

If you have any questions please contact us at 1-800-JANSSEN or at <https://www.janssenmd.com>.

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 **Xarelto®**
rivaroxaban
tablets & oral suspension