Media contacts:
Alayna Shamy
Mobile: (732) 515-8741
ashamy1@its.jnj.com

Joy-Lee Pasqualoni
Mobile: (609) 608-2535
LPasqua7@its.jnj.com

Investor contact:
Jennifer McIntyre
Office: (732) 524-3922

FDA Approves Two New Indications for XARELTO® (rivaroxaban) to Help Prevent and Treat Blood Clots in Pediatric Patients

XARELTO® is available as both an oral tablet and oral suspension formulation for use in appropriate children less than 18 years of age

Convenient oral suspension formulation advances standard of care for children; alleviates administration challenges found with injectable alternatives

XARELTO® now has 11 indications, the most of any direct oral anticoagulant (DOAC), and is the only Factor Xa anticoagulant to offer flexible weight-based dosing for pediatric patients

RARITAN, NJ, Dec. 20, 2021 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today that the U.S. Food and Drug Administration (FDA) has approved two pediatric indications for XARELTO® (rivaroxaban): the treatment of venous thromboembolism (VTE, or blood clots) and reduction in the risk of recurrent VTE in patients from birth to less than 18 years after at least five days of initial parenteral (injected or intravenous) anticoagulant treatment; and thromboprophylaxis (prevention of blood clots and blood-clot related events) in children aged two years and older with congenital heart disease who have undergone the Fontan procedure. XARELTO® is the only direct oral anticoagulant (DOAC) FDA-approved for primary prevention of clots in pediatric patients following

the Fontan procedure and the only DOAC in the U.S. to offer an oral suspension formulation for flexible, body weight-adjusted dosing options for pediatric patients.

CLICK TO TWEET: #BREAKINGNEWS: @US_FDA approves @JanssenUS therapy for the treatment and prevention of #bloodclots in #pediatric patients, providing an alternative to injectable anticoagulants that have long been the standard of care. Learn more: https://bit.ly/3E9qAOk

While VTE more commonly occurs in adults, blood clots can still be a serious problem in children, affecting approximately 58 per 10,000 of those hospitalized in the U.S., with rates increasing.[1] Children may be at greater risk of blood clots when suffering from other conditions, such as infectious diseases, active cancer, or after undergoing surgery, like the Fontan procedure, which is performed in children who have a single functioning heart ventricle to redirect blood flow from the lower body to the lungs.[2,3]

Current medical guidelines are limited and recommend that young patients with or at risk for developing blood clots be treated with standard anticoagulation therapy, such as warfarin or heparin.[4] Often times, physicians have to adjust adult doses, based on limited data for these therapies for younger patients.[4] Additionally, for some of these treatment options, that can mean painful injections, dietary restrictions and regular laboratory monitoring – all things that can be especially challenging for younger patients and their caregivers.[4,5,6]

"Historically, there has been limited guidance and options for healthcare providers on how to help reduce potentially serious, even fatal, blood clots and related events in young children," said Andrew Van Bergen, M.D., Pediatric Cardiologist, Advocate Children's Hospital.* "We have had to adjust adult doses of standard anticoagulation therapies, which are both burdensome and uncomfortable for patients, and require frequent monitoring. Now that XARELTO® is FDA-approved with weight-based dosing options, either as tablets or liquid formulation, a convenient option is

available allowing flexibility to tailor the treatment for my patients. This is a major advancement in antithrombotic care for those patients under the age of 18."

The oral suspension formulation will be administered through a color-coded dosing device that was designed to help minimize dosing errors and is expected to become available in the U.S. for pediatric patients in mid-January 2022. The oral tablets are currently available in the U.S. for appropriate pediatric patients.

"When a child is experiencing health challenges, learning that they are also at risk for a blood clot can feel overwhelming for the patient, and also their parents or caregivers," said Andrea Baer, MS, BCPA, Executive Director of The Mended Hearts, Inc., a patient advocacy organization whose program Mended Little Hearts serves patients and families with congenital heart disease.** "Knowing that there is now an FDA-approved oral treatment option to reduce the risk of blood clots that's easy and may be more comfortable than injections to administer may help ease that burden."

CLICK TO TWEET: #DYK Certain children are at risk for potential #bloodclots? Learn more about a new treatment option from @JanssenUS that provides weight-based dosing: https://bit.ly/3E9qAOk

XARELTO® now has 11 indications in the U.S. – the most of any DOAC – and is the most studied oral Factor Xa inhibitor in its class. This latest approval is based on two Phase 3 pediatric studies from the industry-leading EXPLORER clinical research program, EINSTEIN-Jr, the largest study to date evaluating pediatric patients from birth to <18 years of age with previously diagnosed VTE; and UNIVERSE, the first clinical trial to examine a DOAC for the prevention of VTE in pediatric patients after recently undergoing the Fontan procedure.[7,8]

"Today's FDA approval marks two new XARELTO® indications for pediatric patients, an often underrecognized, but especially important patient population," said James List, M.D., Ph.D., Global Therapeutic Area Head, Cardiovascular, Metabolism, &

Retina, Janssen Research & Development, LLC. "At Janssen, we are committed to addressing unmet medical needs and the approval of the 10th and 11th indications for XARELTO® underscores its capability in reducing the risk of blood clots and cardiovascular events in patients from young to old and with a variety of conditions."

In 2021, Janssen's development partner, Bayer, received approval for XARELTO® in Canada, the European Union, the United Kingdom, Japan, Switzerland and in various Latin American countries for the treatment of VTE and prevention of VTE recurrence in the pediatric population, from birth to adolescents less than 18 years after at least five days of initial parenteral anticoagulation treatment.

About EINSTEIN-Jr

EINSTEIN-Jr was a randomized, multicenter, active-controlled, open-label Phase 3 study that evaluated the use of XARELTO® in 500 children, aged birth to 17 years, with previously diagnosed acute VTE who had started parenteral anticoagulation therapy. Participants were enrolled from November 2014 to September 2018, from 107 sites in 28 countries, and were assigned in a 2:1 ratio to receive either an open-label, body weight-adjusted dose of XARELTO® to approximate a 20-mg adult dose (tablets or a new oral suspension) (n=335) or standard anticoagulation therapy (n=165). EINSTEIN-Jr is the largest pediatric study completed to date in the entire pediatric age population for the treatment of VTE. It is part of the comprehensive EINSTEIN program, which also included four pivotal Phase 3 studies in adult populations: EINSTEIN-DVT, EINSTEIN-PE, EINSTEIN-EXT and EINSTEIN CHOICE.

About UNIVERSE

UNIVERSE was a randomized, multicenter, open-label, active-controlled, two-part, Phase 3 study that examined the use of a novel, oral suspension XARELTO® formulation in children 2-8 years old with single ventricle physiology who had the Fontan procedure within four months before enrollment. From November 2016 to June 2019, a total of 112 participants were enrolled across 36 sites in 10 countries.

Part A evaluated the single- and multiple-dose pharmacokinetic (PK) and pharmacodynamic (PD) properties of XARELTO® while Part B evaluated the comparative safety and efficacy of XARELTO® versus aspirin when used for thromboprophylaxis for 12 months.

About EXPLORER

A collaborative effort between Bayer and Janssen, our industry-leading EXPLORER program seeks to generate important clinical evidence on the safety and efficacy of XARELTO® and its potential role in addressing a wide range of critical medical needs. EXPLORER is unmatched by any oral anticoagulant in the Factor Xa inhibitor class in its size, scope and ambition.

WHAT IS XARELTO® (rivaroxaban)?

XARELTO® is a prescription medicine used to:

- reduce the risk of stroke and blood clots in adults who have a medical condition called atrial fibrillation that is not caused by a heart valve problem. With atrial fibrillation, part of the heart does not beat the way it should. This can lead to the formation of blood clots, which can travel to the brain, causing a stroke, or to other parts of the body
- treat blood clots in the veins of your legs (deep vein thrombosis or DVT) or lungs (pulmonary embolism or PE)
- reduce the risk of blood clots happening again in adults who continue to be at risk for DVT or PE after receiving treatment for blood clots for at least 6 months
- help prevent a blood clot in the legs and lungs of adults who have just had hip or knee replacement surgery
- help prevent blood clots in certain adults hospitalized for an acute illness and after discharge, who are at risk of getting blood clots because of the loss of or decreased ability to move around (mobility) and other risks for getting blood clots, and who do not have a high risk of bleeding

XARELTO® is used with low dose aspirin to:

- reduce the risk of serious heart problems, heart attack and stroke in adults with coronary artery disease (a condition where the blood supply to the heart is reduced or blocked)
- reduce the risk of a sudden decrease in blood flow to the legs, major amputation, serious heart problems or stroke in adults with peripheral artery

disease (a condition where the blood flow to the legs is reduced) and includes adults who have recently had a procedure to improve blood flow to the legs.

XARELTO® is used in children to:

- treat blood clots or reduce the risk of blood clots from happening again in children from birth to less than 18 years, after receiving initial treatment with injectable or intravenous medicines used to treat blood clots.
- help prevent blood clots in children 2 years and older with congenital heart disease after the Fontan procedure.

XARELTO® was not studied and is not recommended in children less than 6 months of age who:

- were less than 37 weeks of growth (gestation) at birth
- had less than 10 days of oral feeding, **or**
- had a body weight of less than 5.7 pounds (2.6 kg)

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT XARELTO®?

XARELTO® may cause serious side effects, including:

- **Increased risk of blood clots if you stop taking XARELTO®.** People with atrial fibrillation (an irregular heartbeat) that is not caused by a heart valve problem (nonvalvular) are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. XARELTO® lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking XARELTO®, you may have increased risk of forming a clot in your blood.

Do not stop taking XARELTO® without talking to the doctor who prescribes it for you. Stopping XARELTO® increases your risk of having a stroke. If you have to stop taking XARELTO®, your doctor may prescribe another blood thinner medicine to prevent a blood clot from forming.

- **Increased risk of bleeding.** XARELTO® can cause bleeding which can be serious and may lead to death. This is because XARELTO® is a blood thinner medicine (anticoagulant) that lowers blood clotting. During treatment with XARELTO® you are likely to bruise more easily, and it may take longer for bleeding to stop. You may be at higher risk of bleeding if you take XARELTO® and have certain other medical problems.

You may have a higher risk of bleeding if you take XARELTO® and take other medicines that increase your risk of bleeding, including:

- Aspirin or aspirin-containing products
- Long-term (chronic) use of non-steroidal anti-inflammatory drugs (NSAIDs)
- Warfarin sodium (Coumadin®, Jantoven®)
- Any medicine that contains heparin
- Clopidogrel (Plavix®)
- Selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
- Other medicines to prevent or treat blood clots

Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above.

Call your doctor or get medical help right away if you or your child develop any of these signs or symptoms of bleeding:

- Unexpected bleeding or bleeding that lasts a long time, such as:
  - Nosebleeds that happen often
  - Unusual bleeding from gums
  - Menstrual bleeding that is heavier than normal, or vaginal bleeding
- Bleeding that is severe or you cannot control
- Red, pink, or brown urine
- Bright red or black stools (looks like tar)
- Cough up blood or blood clots
- Vomit blood or your vomit looks like "coffee grounds"
- Headaches, feeling dizzy or weak
- Pain, swelling, or new drainage at wound sites

- **Spinal or epidural blood clots (hematoma).** People who take a blood thinner medicine (anticoagulant) like XARELTO®, and have medicine injected into their spinal and epidural area, or have a spinal puncture, have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:
  - A thin tube called an epidural catheter is placed in your back to give you certain medicine
  - You take NSAIDs or a medicine to prevent blood from clotting
  - You have a history of difficult or repeated epidural or spinal punctures
  - You have a history of problems with your spine or have had surgery on your spine

If you take XARELTO® and receive spinal anesthesia or have a spinal puncture, your doctor should watch you closely for symptoms of spinal or epidural blood clots.

Tell your doctor right away if you have:

- back pain
- tingling
- numbness
- muscle weakness (especially in your legs and feet)
- or loss of control of the bowels or bladder (incontinence)

XARELTO® is not for use in people with artificial heart valves.

XARELTO® is not for use in people with antiphospholipid syndrome (APS), especially with positive triple antibody testing.

Do not take XARELTO® if you or your child:
- Currently have certain types of abnormal bleeding. Talk to your doctor before taking XARELTO® if you currently have unusual bleeding.
- Are allergic to rivaroxaban or any of the ingredients of XARELTO®.

Before taking XARELTO®, tell your doctor about all your medical conditions, including if you or your child:
- Have ever had bleeding problems
- Have liver or kidney problems
- Have antiphospholipid syndrome (APS)
- Are pregnant or plan to become pregnant. It is not known if XARELTO® will harm your unborn baby.
    - **Tell your doctor** right away if you become pregnant during treatment with XARELTO®. Taking XARELTO® while you are pregnant may increase the risk of bleeding in you or in your unborn baby.
    - Females who are able to become pregnant: Talk with your doctor about pregnancy planning during treatment with XARELTO®. Talk with your doctor about your risk for severe uterine bleeding if you are treated with blood thinner medicines, including XARELTO®.
    - If you take XARELTO® during pregnancy, **tell your doctor** right away if you have any signs or symptoms of bleeding or blood loss. **See "What is the most important information I should know about XARELTO®?" for signs and symptoms of bleeding.**
- Are breastfeeding or plan to breastfeed. XARELTO® may pass into your breast milk. Talk to your doctor about the best way to feed your baby during treatment with XARELTO®.

Tell all of your doctors and dentists that you are taking XARELTO®. They should talk to the doctor who prescribed XARELTO® for you before you have any surgery, medical or dental procedure.

Tell your doctor about all the medicines you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some of your other medicines may affect the way XARELTO® works, causing side effects. Certain medicines may increase your risk of bleeding. **See "What is the most important information I should know about XARELTO®?"**

HOW SHOULD I TAKE XARELTO®?

- Take XARELTO® exactly as prescribed by your doctor.
- **Do not change your dose or stop taking XARELTO® unless your doctor tells you to.** Your doctor may change your dose if needed.
- Your doctor will decide how long you should take XARELTO®.
- XARELTO® may need to be stopped for one or more days before any surgery or medical or dental procedure. Your doctor will tell you when to stop taking XARELTO® and when to start taking XARELTO® again after your surgery or procedure.
- If you need to stop taking XARELTO® for any reason, talk to the doctor who prescribed XARELTO® to you to find out when you should stop taking it. Do not stop taking XARELTO® without first talking to the doctor who prescribes it to you.
- If you have difficulty swallowing XARELTO® tablets whole, talk to your doctor about other ways to take XARELTO®.
- Do not run out of XARELTO®. Refill your prescription of XARELTO® before you run out. When leaving the hospital following a hip or knee replacement, be sure that you will have XARELTO® available to avoid missing any doses.
- If you take too much XARELTO®, go to the nearest hospital emergency room or call your doctor right away.

If you take XARELTO® for:

- **Atrial Fibrillation that is not caused by a heart valve problem:**
  - Take XARELTO® **1 time a day with your evening meal.**
  - If you miss a dose of XARELTO®, take it as soon as you remember on the same day. Take your next dose at your regularly scheduled time.
- **Blood clots in the veins of your legs or lungs:**
  - Take XARELTO® **1 or 2 times a day** as prescribed by your doctor.
  - For the **10-mg dose**, XARELTO® **may be taken with or without food.**
  - For the **15-mg and 20-mg doses**, take XARELTO® **with food at the same time each day.**
  - If you miss a dose:
    - **If you take the 15-mg dose of XARELTO® 2 times a day (a total of 30 mg of XARELTO® in 1 day):** Take XARELTO® as soon as you remember on the same day. You may take 2 doses at the same time to make up for the missed dose. Take your next dose at your regularly scheduled time.

- **If you take XARELTO® 1 time a day:** Take XARELTO® as soon as you remember on the same day. Take your next dose at your regularly scheduled time.

- **Hip or knee replacement surgery:**
  - Take XARELTO® 1 time a day with or without food.
  - If you miss a dose of XARELTO®, take it as soon as you remember on the same day. Take your next dose at your regularly scheduled time.
- **Blood clots in people hospitalized for an acute illness:**
  - Take XARELTO® 1 time a day, with or without food, while you are in the hospital and after you are discharged as prescribed by your doctor.
  - If you miss a dose of XARELTO®, take it as soon as you remember on the same day. Take your next dose at your regularly scheduled time.
- **Reducing the risk of serious heart problems, heart attack and stroke in coronary artery disease:**
  - Take XARELTO® 2.5 mg 2 times a day with or without food.
  - If you miss a dose of XARELTO®, take your next dose at your regularly scheduled time.
  - Take aspirin 75 to 100 mg once daily as instructed by your doctor.
- **Reducing the risk of a sudden decrease in blood flow to the legs, major amputation, serious heart problems or stroke in people with peripheral artery disease, including those who have recently had a procedure to improve blood flow to the legs:**
  - Take XARELTO® 2.5 mg 2 times a day with or without food.
  - If you miss a dose of XARELTO®, take your next dose at your regularly scheduled time.
  - Take aspirin 75 to 100 mg once daily as instructed by your doctor.

For children who take XARELTO®

- The dose of XARELTO® depends on your child's body weight and will be calculated by your child's doctor. Your child's doctor will tell you if XARELTO® can be given to your child with or without food.
- The adult caregiver should give the dose.
- If your child is taking the tablet, the tablet should be taken whole and should not be split in an attempt to provide a lower dose of XARELTO®.
- If your child is taking the oral suspension, use the syringes provided in the original carton. The suspension will be prepared by the pharmacy. See the **Instructions for Use** included in the carton on how to properly give a dose of XARELTO® oral suspension to your child.
- Do not switch between the XARELTO® oral suspension or tablet without first talking to your doctor.
- If your child vomits or spits up:
  - right after or within 30 minutes of taking the oral suspension, give a new full dose.

    - more than 30 minutes after taking the oral suspension, do not give the dose again. Give the next dose at the regularly scheduled time.
    - if vomiting or spitting up persists, contact your child's doctor right away.
- If your child misses a dose:
    - If your child is taking XARELTO® 1 time a day, give the dose as soon as you remember on the same day. If this is not possible, skip this dose and give the next dose at the regularly scheduled time.
    - If your child is taking XARELTO® 2 times a day, give the missed morning dose as soon as you remember. You may give the missed morning dose together with the evening dose. However, a missed evening dose can only be taken in the same evening.
    - If your child is taking XARELTO® 3 times a day, skip the missed dose and give the next dose at the regularly scheduled time.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF XARELTO®?

XARELTO® may cause serious side effects:

- See **"What is the most important information I should know about XARELTO®?"**

The most common side effect of XARELTO® in adults was bleeding.

The most common side effects of XARELTO® in children include:

- bleeding
- vomiting
- cough
- inflamed stomach and gut

Call your doctor for medical advice about side effects. **You may report side effects to the FDA at 1-800-FDA-1088.** You may also report side effects to Janssen Pharmaceuticals, Inc., at 1-800-JANSSEN (1-800-526-7736).

Please read full Prescribing Information, including Boxed Warnings, and Medication Guide for XARELTO®.

About the Janssen Pharmaceutical Companies of Johnson & Johnson

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular & Metabolism,

Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology, and Pulmonary Hypertension.

Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenUS and https://twitter.com/JanssenGlobal. Janssen Research & Development, LLC, is one of the Janssen Pharmaceutical Companies of Johnson & Johnson.

Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding rivaroxaban. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Research & Development, LLC, any of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended January 3, 2021, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's most recently filed Quarterly Report on Form 10-Q, and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

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*Dr. Van Bergen is affiliated with Advocate Children's Hospital, which was provided payment for their participation in the Phase 3 UNIVERSE clinical trial.
** The Mended Hearts, Inc. was provided a grant to help support its VTE disease awareness program.

