Empowering Pharmacist-Physician Collaboration

Autoimmune
PrEP In the Pharmacy

Respiratory
Managing Long COVID

Career
Practice LGBTQ+ Inclusive Pharmacy
Patients with CAD and/or PAD are complex.\textsuperscript{1,2} Helping protect them against thrombosis doesn’t have to be.

**INDICATIONS**

XARELTO\textsuperscript{®} (rivaroxaban) is indicated to reduce the risk of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (AF).

There are limited data on the relative effectiveness of XARELTO\textsuperscript{®} and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled.

XARELTO\textsuperscript{®} is indicated for the treatment of deep vein thrombosis (DVT). XARELTO\textsuperscript{®} is indicated for the treatment of pulmonary embolism (PE). XARELTO\textsuperscript{®} is indicated for the reduction in the risk of recurrence of DVT and/or PE in adult patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months.

XARELTO\textsuperscript{®} is indicated for the prophylaxis of DVT, which may lead to PE in adult patients undergoing knee or hip replacement surgery.

**WARNING: [A] PREMATURE DISCONTINUATION OF XARELTO\textsuperscript{®} INCREASES THE RISK OF THROMBOTIC EVENTS, [B] SPINAL/EPIDURAL HEMATOMA**

A. Premature discontinuation of XARELTO\textsuperscript{®} increases the risk of thrombotic events

Premature discontinuation of any oral anticoagulant, including XARELTO\textsuperscript{®}, increases the risk of thrombotic events. If anticoagulation with XARELTO\textsuperscript{®} 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\textsuperscript{®} 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\textsuperscript{®} 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.

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

- Increased Risk of Thrombotic Events after Premature Discontinuation: Premature discontinuation of any oral anticoagulant, including XARELTO\textsuperscript{®}, 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\textsuperscript{®} to warfarin in clinical trials in atrial fibrillation patients. If XARELTO\textsuperscript{®} 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\textsuperscript{®} 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, P2Y 12 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\textsuperscript{®} 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\textsuperscript{®} is not for use for primary VTE prophylaxis in these hospitalized, acutely ill medical patients at high risk of bleeding.

Please read accompanying Brief Summary of full Prescribing Information, including Boxed WARNINGS for XARELTO\textsuperscript{®}.

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Janssen Pharmaceuticals, Inc.
SPINAL/EPIDURAL ANESTHESIA OR PUNCTURE: When neuromuscular anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents of XARELTO®. Placement or removal of an epidural catheter or lumbar puncture is best not be administered earlier than 6 hours after the removal of the catheter. If to reach a sufficiently low anticoagulant effect in each patient is not known. An indwelling 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 signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression

XARELTO® cannot be monitored with standard laboratory testing. Promptly evaluate patients who have had transcatheter aortic valve replacement (TAVR), based on the results of studies with XARELTO®. There are no 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, 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. These patients do not enroll patients with CrCl <30 mL/min or end-stage renal disease [ESRD] on dialysis. Reductive 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, a reduced risk of thrombosis was observed in these patients. In patients with CrCl 15 to <30 mL/min, there is no 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 to <30 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 Acute 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 to <30 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.

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 who have Recent Lower Extremity Revascularization Due to Symptomatic PAD: In these patients, no data are available. Limited clinical data are available for patients with CrCl 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 normal renal function. 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 severe renal impairment.

Use in Patients with Heparin Impairment: No clinical data are available for adult patients with severe renal impairment. Avoid use of XARELTO® in patients with renal impairment due to 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 moderate 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® does not have adequate and well-controlled studies in pregnant women. 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 fever). 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® dosing versus randomized to warfarin. The anticoagulant effect 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 intravenous 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: During anticoagulant therapy, patients with antiphospholipid syndrome (APS) or lupus anticoagulant, and anti-beta 2-glycoprotein I antibodies, treatment with DOACs has been associated with increased rates of 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 thromboembolic events. 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 strong 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.

III. 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 X 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 breastfeeding 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 1 year of age; therefore, avoid use of XARELTO® in these patients. The limited available data on XARELTO® in pediatric patients 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® 2.5-mg tablets in infants and children. For the XARELTO® 2.5-mg tablets, there are no safety, efficacy, and pharmacokinetic/pharmacodynamic data to support the use in pediatric patients.

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 institute appropriate therapy if bleeding complications associated with overdose occur. An agent to reverse the antifactor 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 accompanying Brief Summary of full Prescribing Information, including Boxed WARNINGS for XARELTO®.

**Warnings and Precautions**

**Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation**

XARELTO is indicated to reduce the risk of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation.

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

**Treatment of Deep Venous Thrombosis**

XARELTO is indicated for the treatment of deep vein thrombosis (DVT).

**Treatment of Pulmonary Embolism**

XARELTO is indicated for the treatment of pulmonary embolism (PE).

**Reduction in the Risk of Recurrence of Deep Venous Thrombosis and/or Pulmonary Embolism**

XARELTO is indicated for the reduction in the risk of recurrence of DVT and/or PE in adult patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months.

**Prophylaxis of Deep Venous Thrombosis Following Hip or Knee Replacement Surgery**

XARELTO is indicated for the prophylaxis of DVT, which may lead to PE in adult patients undergoing knee or hip replacement surgery.

**Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thrombotic or Hemorrhagic Complications Not at High Risk of Bleeding**

XARELTO is indicated for the prophylaxis of venous thromboembolism (VTE) and VTE-related death during hospitalization and post hospital discharge in adult patients admitted for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE and not at high risk of bleeding (see Warnings and Precautions and Clinical Studies [14.5] in Full Prescribing Information).

**Reduction of Risk of Major Cardiovascular Events in Patients with Coronary Artery Disease (CAD)**

XARELTO, in combination with aspirin, is indicated to reduce the risk of major cardiovascular events (cardiovascular death, myocardial infarction, and stroke) in adult patients with coronary artery disease.

**Reduction of Risk of Major Thrombotic Vascular Events in Patients with Peripheral Arterial Disease (PAD), Including Patients after Lower Extremity Revascularization due to Symptomatic PAD**

XARELTO, in combination with aspirin, is indicated to reduce the risk of major thrombotic vascular events (myocardial infarction, ischemic stroke, acute limb ischemia, and major amputation of a vascular etiology) in adult patients with PAD, including patients who have recently undergone a lower extremity revascularization procedure due to symptomatic PAD.

**Treatment of Venous Thromboembolism and Reduction in Risk of Recurrent Venous Thromboembolism in Pediatric Patients**

XARELTO is indicated for the treatment of venous thromboembolism (VTE) and the 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.

**Thromboprophylaxis in Pediatric Patients with Congenital Heart Disease after the Fontan Procedure**

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

**Contraindications**

XARELTO is contraindicated in patients with:

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

**Warnings and Precautions**

Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including XARELTO, increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO to warfarin in clinical trials in atrial fibrillation patients. If XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant (see Dosage and Administration [2.3, 2.4] in Full Prescribing Information, Warnings and Precautions, and Clinical Studies [14.1] in Full Prescribing Information).

**Risk of Bleeding**

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

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

Concomitant use of other drugs that impair hemostasis increases the risk of bleeding. These include aspirin, P2Y12 platelet inhibitors, dual antiplatelet therapy, other antithrombotic agents, fibrinolytic therapy, non-steroidal anti-inflammatory drugs (NSAIDs) (see Drug Interactions), selective serotonin reuptake inhibitors, and serotonin noradrenaline reuptake inhibitors.

Concomitant use of drugs that are known combined P-gp and strong CYP3A inhibitors increases rivaroxaban exposure and may increase bleeding risk (see Drug Interactions).

**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 (i.e., undergoing acute, in-hospital cancer treatment), active gastrointestinal ulcer in the three months prior to treatment, 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.

**Reversal of Anticoagulant Effect**

An agent to reverse the anti-factor Xa activity of rivaroxaban is available. Because of high plasma protein binding, rivaroxaban is not dialyzable (see Clinical Pharmacology [12.3] in Full Prescribing Information). Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Use of procoagulant reversal agents, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa, may be considered but has not been evaluated in clinical efficacy and safety studies. Monitoring for the anticoagulation effect of rivaroxaban using a clotting test (PT, INR or aPTT) or anti-factor Xa (FXa) activity is not recommended.

**Spinal/Epidural Anesthesia or Puncture**

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis (see Boxed Warning).

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

An indwelling epidural or intrathecal catheter should not be removed before at least 2 half-lives have elapsed (i.e., 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® [see Clinical Pharmacology (12.3) in Full Prescribing Information]. The next XARELTO® 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.

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

Use in Patients with Renal Impairment

Nonvalvular Atrial Fibrillation

Periodically assess renal function as clinically indicated (i.e., more frequently in situations in which renal function may decline) and adjust therapy accordingly [see Dosage and Administration (2.1) in Full Prescribing Information]. Consider dose adjustment or discontinuation of XARELTO® in patients who develop acute renal failure while on treatment [see Use in Specific Populations].

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE

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 [see Use in Specific Populations].

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 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 [see Use in Specific Populations].

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 [see Use in Specific Populations].

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 the use of XARELTO® in these patients.

There are no clinical data in pediatric patients younger than 1 year with severe renal impairment 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 of XARELTO® in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy since drug exposure and bleeding risk may be increased [see Use in Specific Populations].

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 [see Drug Interactions].

Avoid concomitant use of XARELTO® with drugs that are known combined P-gp and strong CYP3A inducers [see Drug Interactions].

Risk of Pregnancy-Related Hemorrhage

In pregnant women, XARELTO® should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO cannot be monitored with standard laboratory testing. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress) [see Warnings and Precautions and Use in Specific Populations].

Patients with Prosthetic Heart Valves

On the basis of the GALILEO study, use of XARELTO® is not recommended in patients who have had transcatheater aortic valve replacement (TAVR) because patients randomized to XARELTO® experienced higher rates of death and bleeding compared to those randomized to an anti-platelet regimen. The 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 or Patients Who Require Thrombolyis 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 thrombolyis or pulmonary embolectomy.

Increased Risk of Thrombosis in Patients with Triple Positive 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.

ADVERSE REACTIONS

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

• Increased Risk of Stroke After Discontinuation in Nonvalvular Atrial Fibrillation [see Boxed Warning and Warnings and Precautions]

• Bleeding Risk [see Warnings and Precautions]

• Spinal/Epidural Hematoma [see Boxed Warning and Warnings and Precautions]

Clinical Trials Experience

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

During clinical development for the approved indications, 34,947 adult patients were exposed to XARELTO®.

Hemorrhage

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

Nonvalvular Atrial Fibrillation

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

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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO® N=7111 n (%/year)</th>
<th>Warfarin N=7125 n (%/year)</th>
<th>XARELTO® vs. Warfarin (HR 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding*</td>
<td>395 (3.6) 386 (3.5)</td>
<td>1.04 (0.90, 1.20)</td>
<td></td>
</tr>
<tr>
<td>Intracranial Hemorrhage (ICH)</td>
<td>55 (0.5) 84 (0.7)</td>
<td>0.67 (0.47, 0.93)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic Stroke†</td>
<td>38 (0.3) 58 (0.5)</td>
<td>0.63 (0.42, 0.96)</td>
<td></td>
</tr>
<tr>
<td>Other ICH</td>
<td>19 (0.2) 26 (0.2)</td>
<td>0.74 (0.41, 1.34)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal (GI)†</td>
<td>221 (2.0) 140 (1.2)</td>
<td>1.61 (1.30, 1.99)</td>
<td></td>
</tr>
<tr>
<td>Fatal bleeding*</td>
<td>27 (0.2) 55 (0.5)</td>
<td>0.50 (0.31, 0.79)</td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>24 (0.2) 42 (0.4)</td>
<td>0.58 (0.35, 0.96)</td>
<td></td>
</tr>
<tr>
<td>Non-intracranial</td>
<td>3 (0.0) 13 (0.1)</td>
<td>0.23 (0.07, 0.82)</td>
<td></td>
</tr>
</tbody>
</table>

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

* Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment.
Table 2 shows the number of patients experiencing major bleeding events in duration of treatment was 208 days for XARELTO-treated patients and 204 days for enoxaparin/Vitamin K antagonist (VKA) incidence rates of 1.7% vs. 1.5%, respectively. The mean discontinuation were bleeding events, with XARELTO vs. enoxaparin/Vitamin K. Studies, the most frequent adverse reactions leading to permanent drug discontinuation was bleeding events, with XARELTO vs. enoxaparin/Vitamin K. The mean duration of treatment was 293 days for XARELTO 10 mg-treated patients and 286 days for aspirin 100 mg-treated patients.

Reduction in the Risk of Recurrence of DVT and/or PE

In the EINSTEIN CHOICE clinical study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 1% for XARELTO 10 mg, 2% for XARELTO 20 mg, and 1% for acetylsalicylic acid (aspirin) 100 mg. The mean duration of treatment was 293 days for XARELTO 10 mg-treated patients and 286 days for aspirin 100 mg-treated patients.

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

Table 3: Bleeding Events* in EINSTEIN CHOICE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO® 10 mg N=1127 n (%)</th>
<th>Acetylsalicylic Acid (aspirin)® 100 mg N=1131 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding event</td>
<td>5 (0.4)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Non-fatal critical organ bleeding</td>
<td>2 (0.2)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Non-fatal non-critical organ bleeding</td>
<td>3 (0.3)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Clinically relevant non-major (CRNM) bleeding</td>
<td>22 (2.0)</td>
<td>20 (1.8)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>151 (13.4)</td>
<td>138 (12.2)</td>
</tr>
</tbody>
</table>

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

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

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

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

In the EINSTEIN CHOICE study, there was an increased incidence of bleeding, including major and CRNM bleeding in the XARELTO 20 mg group compared to the XARELTO 10 mg or aspirin 100 mg groups.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

In the RECORD clinical trials, the overall incidence rate of adverse reactions leading to permanent treatment discontinuation was 3.7% with XARELTO.

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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO® 10 mg N=4467 n (%)</th>
<th>Enoxaparin® N=4524 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding event</td>
<td>14 (0.3)</td>
<td>9 (0.2)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding into a critical organ</td>
<td>2 (&lt;0.1)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Bleeding that required re-operation</td>
<td>7 (0.2)</td>
<td>5 (0.1)</td>
</tr>
<tr>
<td>Extra-surgical site bleeding requiring transfusion of &gt;2 units of whole blood or packed red blood cells</td>
<td>4 (0.1)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Any bleeding event</td>
<td>261 (5.8)</td>
<td>251 (5.6)</td>
</tr>
</tbody>
</table>

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

Treatment of Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE)

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

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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO® 10 mg N=4130 n (%)</th>
<th>Enoxaparin/ VKA N=4116 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding event</td>
<td>40 (1.0)</td>
<td>72 (1.7)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>3 (&lt;0.1)</td>
<td>8 (0.2)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>2 (&lt;0.1)</td>
<td>4 (&lt;0.1)</td>
</tr>
<tr>
<td>Non-fatal critical organ bleeding</td>
<td>10 (0.2)</td>
<td>29 (0.7)</td>
</tr>
<tr>
<td>Intracranial†</td>
<td>3 (&lt;0.1)</td>
<td>10 (0.2)</td>
</tr>
<tr>
<td>Retroperitoneal‡</td>
<td>1 (&lt;0.1)</td>
<td>6 (0.2)</td>
</tr>
<tr>
<td>Intracranial‡</td>
<td>3 (&lt;0.1)</td>
<td>2 (&lt;0.1)</td>
</tr>
<tr>
<td>Intracranial‡</td>
<td>0</td>
<td>4 (&lt;0.1)</td>
</tr>
<tr>
<td>Non-fatal non-critical organ bleeding</td>
<td>27 (0.7)</td>
<td>37 (0.9)</td>
</tr>
<tr>
<td>Decrease in Hb ≥ 2 g/dL</td>
<td>28 (0.7)</td>
<td>42 (1.0)</td>
</tr>
<tr>
<td>Transfusion of &gt;2 units of whole blood or packed red blood cells</td>
<td>18 (0.4)</td>
<td>25 (0.6)</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>357 (8.6)</td>
<td>357 (8.7)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>1169 (28.3)</td>
<td>1153 (28.0)</td>
</tr>
</tbody>
</table>

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

† Treatment schedule: XARELTO 10 mg once daily or aspirin 100 mg once daily.

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

In the EINSTEIN CHOICE study, there was an increased incidence of bleeding, including major and CRNM bleeding in the XARELTO 20 mg group compared to the XARELTO 10 mg or aspirin 100 mg groups.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

In the RECORD clinical trials, the overall incidence rate of adverse reactions leading to permanent treatment discontinuation was 3.7% with XARELTO.

The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown in Table 4.
Table 4: Bleeding Events* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1-3) (continued)

<table>
<thead>
<tr>
<th>Hip Surgery Studies</th>
<th>XARELTO 10 mg N=3281 n (%)</th>
<th>Enoxaparin† N=3298 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding event</td>
<td>7 (0.2)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding into a critical organ</td>
<td>1 (&lt;0.1)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Bleeding that required re-operation</td>
<td>2 (0.1)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Extra-surgical site bleeding requiring transfusion of ≥2 units of whole blood or packed cells</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Any bleeding event†</td>
<td>201 (6.1)</td>
<td>191 (5.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Knee Surgery Study</th>
<th>XARELTO 40 mg / placebo N=3299 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding event</td>
<td>7 (0.6)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding into a critical organ</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Bleeding that required re-operation</td>
<td>5 (0.4)</td>
</tr>
<tr>
<td>Extra-surgical site bleeding requiring transfusion of ≥2 units of whole blood or packed cells</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Any bleeding event†</td>
<td>60 (5.0)</td>
</tr>
</tbody>
</table>

* Bleeding events occurring anytime following the first dose of double-blind study medication (which may have been prior to administration of active drug) until two days after the last dose of double-blind study medication. Patients may have more than one event.
† Includes the placebo-controlled period for RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)
‡ Includes major bleeding events

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

Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding

In the MAGELLAN study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events. Cases of pulmonary hemorrhage and pulmonary hemorrhage with bronchiectasis were observed. Patients with bronchiectasis/pulmonary cavitation, active cancer (i.e., undergoing acute, in-hospital cancer treatment), dual antiplatelet therapy or active gastrointestinal ulcer or any bleeding in the previous three months had an excess of bleeding with XARELTO compared with enoxaparin/placebo and are excluded from all MAGELLAN data presented in Table 5. The incidence of bleeding leading to drug discontinuation was 2.5% for XARELTO vs. 1.4% for enoxaparin/placebo.

Table 5 shows the number of patients experiencing various types of bleeding events in the MAGELLAN study.

Table 5: Bleeding Events in MAGELLAN* Study—Safety Analysis Set—On Treatment Plus 2 Days

<table>
<thead>
<tr>
<th>MAGELLAN Study†</th>
<th>XARELTO 10 mg N=3218 n (%)</th>
<th>Enoxaparin 40 mg / placebo N=3239 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding²</td>
<td>22 (0.7)</td>
<td>15 (0.5)</td>
</tr>
<tr>
<td>Critical site bleeding</td>
<td>7 (0.2)</td>
<td>4 (0.1)</td>
</tr>
<tr>
<td>Fatal bleeding³</td>
<td>3 (&lt;0.1)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding events (CRNM)</td>
<td>93 (2.9)</td>
<td>34 (1.1)</td>
</tr>
</tbody>
</table>

* Patients at high risk of bleeding (i.e. bronchiectasis/pulmonary cavitation, active cancer, dual antiplatelet therapy or active gastrointestinal ulcer or any bleeding in the previous three months) were excluded.
† Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment.
‡ Defined as clinically overt bleeding associated with a drop 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.
³ Fatal bleeding is adjudicated death with the primary cause of death from bleeding.

Patients received either XARELTO or placebo once daily for 35 ±4 days starting in hospital and continuing post hospital discharge or received enoxaparin or placebo once daily for 10 ±4 days in the hospital.

Table 6: Major Bleeding Events in COMPASS—On Treatment Plus 2 Days*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO N=1034 n (%/year)</th>
<th>Placebo N=1017 n (%/year)</th>
<th>XARELTO vs. Placebo HR (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified ISTH Major Bleeding²</td>
<td>263 (1.6)</td>
<td>144 (0.9)</td>
<td>1.8 (1.5, 2.3)</td>
</tr>
<tr>
<td>- Fatal bleeding event Intracranial hemorrhage (ICH)</td>
<td>12 (&lt;0.1)</td>
<td>8 (&lt;0.1)</td>
<td>1.5 (0.6, 3.7)</td>
</tr>
<tr>
<td>- Non-intracranial</td>
<td>6 (&lt;0.1)</td>
<td>3 (&lt;0.1)</td>
<td>2.0 (0.5, 8.0)</td>
</tr>
<tr>
<td>- Symptomatic bleeding in critical organ (non-fatal)</td>
<td>58 (0.3)</td>
<td>43 (0.3)</td>
<td>1.4 (0.9, 2.0)</td>
</tr>
<tr>
<td>- ICH (fatal and non-fatal)</td>
<td>23 (0.1)</td>
<td>21 (0.1)</td>
<td>1.1 (0.6, 2.0)</td>
</tr>
<tr>
<td>- Hemorrhagic Stroke Other ICH</td>
<td>18 (0.1)</td>
<td>13 (0.1)</td>
<td>1.4 (0.7, 2.8)</td>
</tr>
<tr>
<td>- Bleeding into the surgical site requiring reoperation (non-fatal, not in critical organ)</td>
<td>7 (0.1)</td>
<td>6 (&lt;0.1)</td>
<td>1.2 (0.4, 3.5)</td>
</tr>
<tr>
<td>- Bleeding leading to hospitalization (non-fatal, not in critical organ, not requiring reoperation)</td>
<td>188 (1.1)</td>
<td>91 (0.5)</td>
<td>2.1 (1.6, 2.7)</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>117 (0.7)</td>
<td>49 (0.3)</td>
<td>2.4 (1.7, 3.4)</td>
</tr>
</tbody>
</table>

* Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment in the safety analysis set in COMPASS patients.
† Treatment schedule: XARELTO 2.5 mg twice daily or placebo. All patients received background therapy with aspirin 100 mg once daily.
‡ Defined as i) fatal bleeding, or ii) symptomatic bleeding in a critical area or organ, such as intraarticular, intramuscular with compartment syndrome, intraspinal, intracranial, intravascular, respiratory, pericardial, liver, pancreas, retroperitoneal, adrenal gland or kidney; or iii) bleeding into the surgical site requiring reoperation, or iv) bleeding leading to hospitalization.

Table 7: Major Bleeding Events* in VOYAGER—On Treatment Plus 2 Days

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO N=3256 n (%) Event rate %/year</th>
<th>Placebo N=3248 n (%) Event rate %/year</th>
<th>XARELTO vs. Placebo HR (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI Major Bleeding (CABG/non-CABG)</td>
<td>62 (1.9)</td>
<td>0.96 (1.4)</td>
<td>0.67 (1.0, 2.1)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>6 (0.2)</td>
<td>0.09 (0.2)</td>
<td>0.09 (1.0, 3.3, 2)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>13 (0.4)</td>
<td>0.20 (0.7)</td>
<td>0.26 (0.4, 1.6)</td>
</tr>
<tr>
<td>Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or in hematocrit of ≥15%</td>
<td>46 (1.4)</td>
<td>0.71 (2.0)</td>
<td>0.36 (1.2, 3.2)</td>
</tr>
</tbody>
</table>

* Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories.
XARELTO® (rivaroxaban)

1 Treatment schedule: XARELTO 2.5 mg twice daily or placebo. All patients received background therapy with aspirin 100 mg once daily.

CABG: Coronary artery bypass graft; CI: confidence interval; HR: hazard ratio; TIMI: Thrombolysis in Myocardial Infarction

Bleeding Criteria

Other Adverse Reactions

Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in the EINSTEIN DVT and EINSTEIN PE studies are shown in Table 8.

Table 8: Other Adverse Reactions* Reported by ≥1% of XARELTO-Treated Patients in EINSTEIN DVT and EINSTEIN PE Studies

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>XARELTO N=1718 (n (%))</th>
<th>Enoxaparin/VKA N=1711 (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain</td>
<td>46 (2.7)</td>
<td>25 (1.5)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>24 (1.4)</td>
<td>15 (0.9)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain</td>
<td>50 (2.9)</td>
<td>31 (1.8)</td>
</tr>
<tr>
<td></td>
<td>Muscle spasm</td>
<td>23 (1.3)</td>
<td>13 (0.8)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>38 (2.2)</td>
<td>22 (1.3)</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>24 (1.4)</td>
<td>11 (0.6)</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>20 (1.2)</td>
<td>10 (0.6)</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td>28 (1.6)</td>
<td>18 (1.1)</td>
</tr>
<tr>
<td>EINSTEIN PE Study</td>
<td>XARELTO N=2412 (n (%))</td>
<td>Enoxaparin/VKA N=2405 (n (%))</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus</td>
<td>53 (2.2)</td>
<td>27 (1.1)</td>
</tr>
</tbody>
</table>

* Adverse reaction with Relative Risk >1.5 for XARELTO versus comparator.

Table 9: Other Adverse Drug Reactions* Reported by ≥1% of XARELTO-Treated Patients in RECORD 1-3 Studies

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>XARELTO N=4487 (n (%))</th>
<th>Enoxaparin N=6524 (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Wound secretion</td>
<td>125 (2.8)</td>
<td>89 (2.0)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Pain in extremity</td>
<td>74 (1.7)</td>
<td>55 (1.2)</td>
</tr>
<tr>
<td></td>
<td>Muscle spasm</td>
<td>52 (1.2)</td>
<td>32 (0.7)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Syncope</td>
<td>55 (1.2)</td>
<td>32 (0.7)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus</td>
<td>96 (2.1)</td>
<td>79 (1.8)</td>
</tr>
<tr>
<td></td>
<td>Blister</td>
<td>63 (1.4)</td>
<td>40 (0.9)</td>
</tr>
</tbody>
</table>

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

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

Pediatric Patients

Treatment of Venous Thromboembolism and Reduction in Risk of Recurrent Venous Thromboembolism in Pediatric Patients

The safety assessment is based on data from the EINSTEIN Junior Phase 3 study in 491 patients from birth to less than 18 years of age. Patients were randomized 2:1 to receive body weight-adjusted doses of XARELTO or comparator (unfractionated heparin, low molecular weight heparin, fondaparinux or VKA).

Discontinuation due to bleeding events occurred in 6 (1.8%) patients in the XARELTO group and 3 (1.9%) patients in the comparator group.

Table 10: Bleeding Events in EINSTEIN Junior Study – Safety Analysis Set - Main Treatment Period†

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO group N=329 (n (%))</th>
<th>Comparator group N=162 (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding†</td>
<td>0 (0.0)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding†</td>
<td>10 (3.0)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Trivial bleeding</td>
<td>113 (34.3)</td>
<td>44 (27.2)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>119 (36.2)</td>
<td>45 (27.8)</td>
</tr>
</tbody>
</table>

† These events occurred after randomization until 3 months of treatment (1 month for patients <2 years with central venous catheter-related VTE (CVC-VTE). Patients may have more than one event.

Table 11: Other Adverse Reactions* Reported in XARELTO-Treated Patients by ≥5% in EINSTEIN Junior Study

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>XARELTO N=329 (n (%))</th>
<th>Comparator group N=162 (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain in extremity</td>
<td>23 (7)</td>
<td>7 (4.3)</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>23 (7)</td>
<td>7 (4.3)</td>
</tr>
</tbody>
</table>

* Adverse reaction with Relative Risk >1.5 for XARELTO versus comparator.

T:10.75" B:11"

Table 12: Bleeding Events in UNIVERSE Study - Safety Analysis Set - On Treatment Plus 2 Days

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XARELTO N=64 (n (%))</th>
<th>Aspirin N=36 (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding†</td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis leading to transfusion</td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Clinically relevant non-major (CRNM) bleeding‡</td>
<td>4 (6.3)</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Trivial bleeding</td>
<td>21 (32.8)</td>
<td>12 (35.3)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>23 (35.9)</td>
<td>14 (41.2)</td>
</tr>
</tbody>
</table>

‡ Defined as 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.

Table 10 shows the number of patients experiencing bleeding events in the EINSTEIN Junior study. In female patients who had experienced menarche, ages 12 to <18 years of age, menorrhagia occurred in 23 (27%) female patients in the XARELTO group and 5 (10%) female patients in the comparator group.

Table 12 shows the number of patients experiencing bleeding events in the UNIVERSE study.
**DRUG INTERACTIONS**

**General Induction and Inhibition Properties**

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Combined P-gp and strong CYP3A inhibitors increase exposure to rivaroxaban and may increase the risk of bleeding. Combined P-gp and strong CYP3A inducers decrease exposure to rivaroxaban and may decrease the risk of thromboembolic events.

**Drugs that Inhibit Cytochrome P450 3A Enzymes and Drug Transport Systems**

Interaction with Combined P-gp and Strong CYP3A Inhibitors

Avoid concomitant administration of XARELTO with known combined P-gp and strong CYP3A inhibitors [e.g., ketoconazole and ritonavir] [see Warnings and Precautions and Clinical Pharmacology (12.3) in Full Prescribing Information]. Although clinical studies have been conducted with a combined P-gp and strong CYP3A inhibitor, pharmacokinetic data suggest that no precautions are necessary with concomitant administration with XARELTO as the change in exposure is unlikely to affect the bleeding risk [see Clinical Pharmacology (12.3) in Full Prescribing Information].

Interaction with Combined P-gp and Moderate CYP3A Inhibitors in Patients with Renal Impairment

XARELTO should not be used in patients with CrCl 15 to <80 mL/min who are unlikely to affect the bleeding risk [see Clinical Pharmacology (12.3) in Full Prescribing Information].

**Drugs that Induce Cytochrome P450 3A Enzymes and Drug Transport Systems**

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A inducers [e.g., carbamazepine, phenytoin, rifampin, St. John’s wort] [see Warnings and Precautions and Clinical Pharmacology (12.3) in Full Prescribing Information].

**Anticoagulants and NSAIDs/Aspirin**

Administration of enoxaparin, warfarin, aspirin, clopidogrel and chronic NSAID use may increase the risk of bleeding [see Clinical Pharmacology (12.3) in Full Prescribing Information].

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

**Anticoagulants and NSAIDs/Aspirin**

- 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

**Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of XARELTO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Blood and lymphatic system disorders: agranulocytosis, thrombocytopenia Hepatobiliary disorders: jaundice, cholestasis, hepatitis [including hepatocellular injury] Immune system disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema Nervous system disorders: hemiparesis Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS)

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

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 XARELTO to a pregnant woman [see Warnings and Precautions].

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. The U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

**Clinical Considerations**

**Disease-Associated Maternal and/or Embryo/Fetal Risk**

Pregnancy is a risk factor for venous thromboembolism and that risk is increased in women with inherited or acquired thrombophilias. Women with thromboembolic disease have an increased risk of maternal complications including pre-eclampsia. Maternal thromboembolic disease increases the risk for intrauterine growth restriction, placental abruption and early and late pregnancy loss.

**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**

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding and this risk may be increased during labor or delivery [see Warnings and Precautions]. The risk of bleeding should be balanced with the risk of thrombotic events when considering the use of XARELTO in this setting.

**Data**

**Human Data**

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. In an in vitro placenta perfusion model, unbound rivaroxaban was rapidly transferred across the human placenta.

**Animal Data**

Rivaroxaban crosses the placenta in animals. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant rabbits were given oral doses of >10 mg/kg rivaroxaban during the period of organogenesis. This dose corresponds to about 4 times the human exposure of unbound drug, based on AUC comparisons at the highest recommended human dose of 20 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg during the period of organogenesis. This dose corresponds to about 14 times the human exposure of unbound drug. In rats, peripartal maternal bleeding and maternal and fetal death occurred at the rivaroxaban dose of 40 mg/kg (about 6 times maximum human exposure of the unbound drug at the human dose of 20 mg/day).

**Lactation**

**Risk Summary**

Rivaroxaban has been detected in human milk. There is insufficient data to determine the effects of rivaroxaban on the breastfed child or on milk production. Rivaroxaban and/or its metabolites were present in the milk of rats. The developmental and health benefits of breastfeeding should be considered 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 [see Data].

**Data**

**Animal Data**

Following a single oral administration of 3 mg/kg of radioactive [14C]-rivaroxaban to lactating rats between Day 8 to 10 postpartum, the concentration of total radioactivity was determined in milk samples collected up to 32 hours post-dose. The estimated amount of radioactivity excreted with milk within 32 hours after administration was 2.1% of the maternal dose.

**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

The safety and effectiveness of XARELTO have been established in pediatric patients from birth to less than 18 years for the treatment of VTE and the reduction in risk of recurrent VTE. Use of XARELTO is supported in these age groups by evidence from adequate and well-controlled studies of XARELTO in adults with additional pharmacokinetic, safety and efficacy data from a multicenter, prospective, open-label, active-controlled randomized study in pediatric patients, their parents or guardians, with moderate renal impairment (CrCl 30 to <50 mL/min) [see Clinical Pharmacology (12.3) and Clinical Studies (14.9) in Full Prescribing Information].

The safety and effectiveness of XARELTO have been established for use in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure. Use of XARELTO is supported in these age groups by evidence from adequate and well-controlled studies of XARELTO in adults with additional data from a multicenter, prospective, open-label, active controlled study in 112 pediatric patients to evaluate the single- and multiple-dose pharmacokinetic properties of XARELTO and the safety and efficacy of XARELTO when used for thromboprophylaxis for 12 months in children with single ventricle physiology who had the Fontan procedure [see Dosage and Administration (2.2) in Full Prescribing Information, Adverse Reactions, Clinical Pharmacology (12.3) and Clinical Studies (14.9) in Full Prescribing Information].

Clinical studies that evaluated safety, efficacy, pharmacokinetic and 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, pharmacokinetic and 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

Of the total number of adult patients in clinical trials for the approved indications of XARELTO (N=61434 patients), 27 percent 75 years and over, with 27 percent 75 years and over. 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 (see Clinical Pharmacology (12.3) and Clinical Studies (14) in Full Prescribing Information).

Renal Impairment

In pharmacokinetic studies, compared to healthy adult subjects with normal creatinine clearance, rivaroxaban exposure increased by approximately 44 to 84% in adult subjects with renal impairment. Increases in pharmacodynamic effects were also observed [see Clinical Pharmacology (12.3) in Full Prescribing Information].

Nonvalvular Atrial Fibrillation

Patients with Chronic Kidney Disease not on Dialysis

In the ROCKET AF trial, patients with CrCl 30 to 50 mL/min were administered XARELTO 15 mg once daily resulting in serum concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in the ROCKET AF study [see Clinical Pharmacology (12.2, 12.3) in Full Prescribing Information]. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with moderate renal impairment [see Clinical Pharmacology (12.3) in Full Prescribing Information].

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with XARELTO did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of XARELTO 2.5 mg twice daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those in patients with moderate renal impairment [see Clinical Pharmacology (12.3) in Full Prescribing Information] and Clinical Studies (14) in Full Prescribing Information] and Clinical Studies (14) in Full Prescribing Information].

In the EINSTEIN trials, patients with CrCl values <30 mL/min at screening were excluded from the studies, but administration of XARELTO is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to <50 mL/min) [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 15 to <30 mL/min. Avoid the use of XARELTO in patients with CrCl <15 mL/min.

Prophylaxis of DVT Following Hip or Knee Replacement Surgery

The combined analysis of the RECORD 1-3 clinical efficacy studies did not show an increase in bleeding risk for patients with CrCl 30 to 50 mL/min and reported a possible increase in total venous thromboembolism in this population. In the RECORD 1-3 trials, patients with CrCl values <30 mL/min at screening were excluded from the studies, but administration of XARELTO 10 mg once daily is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to <50 mL/min) [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 15 to <30 mL/min. Avoid the use of XARELTO in patients with CrCl <15 mL/min.

Risk for Thromboembolic Combinations Not at High Risk of Bleeding

Patients with CrCl values <30 mL/min at screening were excluded from the MAGELLAN study. In patients with CrCl <30 mL/min a dose of XARELTO 10 mg once daily is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to <50 mL/min) [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 15 to <30 mL/min. Avoid the use of XARELTO in patients with CrCl <15 mL/min.

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

Patients with Chronic Kidney Disease not on Dialysis

Patients with a CrCl <15 mL/min at screening were excluded from COMPASS and VOYAGER, 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) [see Clinical Pharmacology (12.3) in Full Prescribing Information], whose efficacy and safety outcomes were similar to those with preserved renal function.

Patients with End-Stage Renal Disease on Dialysis

No clinical outcome data are available for the use of XARELTO with aspirin in patients with ESRD on dialysis since these patients were not enrolled in COMPASS or VOYAGER. In patients with ESRD maintained on intermittent hemodialysis, administration of XARELTO 2.5 mg twice daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in moderate renal impaired patients in the COMPASS study [see Clinical Pharmacology (12.2, 12.3) in Full Prescribing Information]. It is not known whether these concentrations will lead to similar CV risk reduction and bleeding risk in patients with ESRD on dialysis as was seen in COMPASS.

Pediatric Use

No dosage adjustment is required in patients 1 year of age or older with mild renal impairment (eGFR 50 to ≤80 mL/min/1.73 m²). 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 the use of XARELTO in these patients.

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

Avoid the use of XARELTO in patients with moderate hepatic impairment (Child-Pugh B). The safety or PK of XARELTO in patients with severe hepatic impairment (Child-Pugh C) has not been evaluated [see Clinical Pharmacology (12.3) in Full Prescribing Information].

Hepatic Impairment

In a pharmacokinetic study, compared to healthy adult subjects with normal liver function, AUC increases of 127% were observed in adult subjects with severe (Child-Pugh C) hepatic impairment [see Clinical Pharmacology (12.3) in Full Prescribing Information].

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

No clinical data are available in pediatric patients with hepatic impairment.

OVERDOSE

Overdose of XARELTO may lead to hemorrhage. Discontinue XARELTO and initiate appropriate therapy if bleeding complications associated with overdose occur. Rivaroxaban systemic exposure is not further increased at rivaroxaban doses >56 mg due to limited absorption. The use of activated charcoal to reduce absorption in case of XARELTO overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not dialyzable [see Warnings and Precautions and Clinical Pharmacology (12.3) in Full Prescribing Information]. Partial reversal of laboratory anticoagulation parameters may be achieved with plasma products. An agent to reverse the anti-factor Xa activity of rivaroxaban is available.

Active Ingredient Made in Germany

Manufactured for:

Janssen Pharmaceuticals, Inc.

Titusville, NJ 08560

Bayer HealthCare AG

51388 leverkusen, Germany

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To date, more than 527,000,000 known cases of COVID-191 have been reported worldwide—a number that is likely much higher due to underreporting. Nor does that number include deaths indirectly attributable to COVID-19, such as those of individuals who had medical emergencies but could not receive care or those who were unable to receive routine screenings and other health care procedures.

Now, more than 2 years after the pandemic began, we are beginning to see the impact of COVID-19 over time, including long COVID. Also known as long-haul COVID, postacute COVID-19, long-term effects of COVID, or chronic COVID,2 long COVID includes a constellation of symptoms that last weeks or months after a person has received a SARS-CoV-2 diagnosis. This month, Drug Topics® takes a deeper look at long COVID, including pharmacists’ role in helping patients manage these life-altering symptoms.

Elsewhere in the issue, we share the story of how pharmacy technicians have been integral to the COVID-19 vaccination effort. Since 2017, efforts have been made to expand the role of pharmacy technicians, and the pandemic kicked many of those efforts into overdrive. For example, the PREP Act was amended to allow authorized pharmacy technicians to administer vaccines across the country.

I would also like to extend a thank you to all our readers who attended the virtual Total Pharmacy® Solutions Summit on April 30. This 1-day event saw over 100 attendees tune in to learn from experts and leaders across the independent pharmacy space. We hope that the insights and knowledge shared during the event help improve your pharmacy practice—and if you weren’t able to attend, turn to page 24 for a recap of the day. The next summit will take place this autumn; be sure to register for our Drug Topics® and Total Pharmacy® e-newsletters for updates and announcements.

As always, thank you for reading.

Mike Hennessy Jr
President & CEO

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*Drug Topics*® is the top-ranked pharmacy resource for community and health-system professionals. Since 1857, readers have turned to *Drug Topics*® for coverage of issues and trends important to the practice of pharmacy, and for a forum in which they can share viewpoints and practical ideas for better pharmacy management and patient care.
Easing the Burden of Burnout With Technology

Lani Bertrand, RPh, senior director of commercial integration at Omnicell, joins Drug Topics® to discuss how technology can ease some of the burdens that pharmacists experienced during the COVID-19 pandemic.

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Ramzi Yacoub, PharmD, Chief Pharmacy Officer at SingleCare, joined Drug Topics® to discuss the ins and outs of medication discount cards and coupons.

Wellbeing Checkup: Managing Chronic Stress
Jennifer Bourgeois, PharmD, a clinical pharmacist and founder of Well & Free, LLC, shares her tips for managing chronic stress, prioritizing rest, and practicing self-care as a pharmacist.

We believe that reimbursement for the enhanced patient care and medication use services we provide is the future of community-based pharmacy practice.

—MARK MCCURDY, RPH
Owner, Mark’s Pharmacy, Cambridge, NE
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READ MORE:

June 2022 DrugTopics 13
The role of pharmacy technicians in immunizations has evolved rapidly, particularly over the past 2 years because of COVID-19. Prior to the pandemic, pharmacy technicians for the most part were limited to assisting pharmacists in basic tasks related to immunizations. These included screening patients, preparing for the immunization, and performing administrative tasks required for immunization programs.

In 2016, Idaho led the way in expanding the role of pharmacy technicians to include administering immunizations. Through a pilot program, researchers wanted to evaluate the potential effectiveness of immunization training for pharmacy technicians, and the results were clear: All pharmacy technicians taking part in the study passed their assessments on the first attempt. These same technicians went on to administer 953 immunizations over a 6-month period with zero adverse effects.

The momentum for pharmacy technician-administered immunizations continued in Michigan, Washington state, Rhode Island, Utah, and Nevada. Although pharmacy organizations and advocates, such as the National Pharmacy Technician Association (NPTA), planned for a state-by-state campaign to expand the role of pharmacy technicians in immunization administration, no one could have anticipated what was to come.

In August 2020, with COVID-19 running rampant throughout the country, the US Department of Health and Human Services amended the Public Readiness and Emergency Preparedness (PREP) Act to authorize qualified pharmacy technicians to administer immunizations in all 50 states, regardless of state-specific regulations. These qualifications included completing a training program approved by the Accreditation Council for Pharmacy Education, being nationally certified or registered to practice in the technician's state, having a current certificate in cardiopulmonary resuscitation, and practicing with a licensed pharmacist onsite.

The goal of amending the PREP Act was to help states and US territories meet the demand for COVID-19 vaccines and protect communities as much as possible—a crucial decision as the nation prepared for the largest immunization event in world history. As of this writing, more than 258 million Americans have received at least 1 dose of a COVID-19 vaccine and over 576 million COVID-19 vaccine doses have been administered in the United States. It is inconceivable that this accomplishment could have taken place without pharmacy technicians.

Pharmacy technicians have demonstrated, beyond any doubt or concern, their ability and willingness to play a vital, direct role in the administration of immunizations. So, what happens next? Our focus must now shift to the pending sunset of the authorization prescribed under the PREP Act and what steps the states will take to ensure that qualified, trained pharmacy technicians are permitted to continue serving the public through immunization administration. NPTA believes that the state boards of pharmacy or state legislative bodies where necessary, must act swiftly and decisively to make this a permanent, authorized role for qualified pharmacy technicians—after all, how can anyone justify saying that these individuals were qualified to safely administer immunizations throughout the pandemic but are now no longer qualified because the demand for vaccines is stabilizing? This is a genie that should not and must not be placed back in the bottle.

For references, visit drugtopics.com.

Mike Johnston, CPhT-Adv, is the CEO and founder of the National Pharmacy Technician Association. Edgar Galvan is the director of marketing and communication at The Johnston Group.

NPTA will be rolling out an advocacy campaign across each state to ensure that this occurs. To learn more or become involved in this campaign to ensure that qualified pharmacy technicians will be permitted to continue administering immunizations, scan the QR code.
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HIV remains a significant public health problem in the United States, with new infections frequently occurring. In 2019, a federal response—Ending the HIV Epidemic—was announced, with a goal of drastically decreasing the number of new infections by 2030. Pre-exposure prophylaxis (PrEP) is a once-daily pill to prevent HIV infection. Although PrEP has a more than 90% efficacy rate, it is vastly underused. Pharmacists can provide access to PrEP services in their pharmacies, including sharing information about the therapy, helping patients enroll in a PrEP care program, and coordinating with other health care providers to ensure their patients receive the best possible care. Pharmacists can also address any concerns their patients may have about PrEP and provide support throughout the course of PrEP treatment.

Maria Lopez, PharmD, president of clinical pharmacy service for Mission Wellness Pharmacy, a specialty pharmacy in San Francisco and the first California pharmacy to initiate PrEP, explained that it’s important for pharmacies to offer PrEP because they are accessible and have highly trained medication experts on hand to help. “The COVID-19 pandemic highlighted the ability of pharmacies... to provide access to tests and vaccines. They can utilize their expertise in similar ways for public health to address HIV and STI [sexually transmitted infection] epidemics,” she said.

Kristen Nichols, PharmD, BCPS, BCPPS, BCIDP, an infectious diseases specialist and a senior content management consultant, clinical effectiveness, at Wolters Kluwer, Health, noted there are disparities in the receipt of PrEP along age, race, sex, and geography lines. For example, women are less likely to initiate PrEP, and Black women are less likely to initiate it than White women.

“Access through pharmacies would likely increase the number of patients who are able to get started on PrEP; pharmacists are considered some of the most trustworthy and are the most accessible health care professionals,” she said. “There may be a lower barrier to care entry if a person can get engaged in care at their pharmacy as compared [with] other health care settings.”

“Pharmacies are motivated to sell prescriptions, which means that the system is already in place for encouraging adherence,” Nichols added. “For example, automated refill processes could assist with a vital component of PrEP, which is adherence and retention in therapy.”

Anthony V. Minniti, RPh, co-owner of Bell Pharmacy in Camden, New Jersey—which offers its own PrEP clinic inside—believes pharmacists can really “move the needle” with PrEP in much the same fashion as they did with COVID-19 testing and vaccination. “We came up with a business approach to PrEP as a great opportunity to expand hands-on pharmacy practice,” he said. “We set about creating open access to our patient population back in 2017. We have a big population of those who are in need of PrEP, and we knew we needed to do this to improve access and health care outcomes.”

**Education Matters**

It’s not uncommon for patients to stop taking PrEP within a year of starting—or for patients to not take the medication as prescribed.

“Pharmacists are uniquely positioned to educate patients [and] help them overcome barriers to medication adherence—which is extremely important for it to prevent HIV infection—as well as social and economic barriers,” Lopez said. “Pharmacies often sell condoms, so having access to PrEP is a vital part of the whole package.”

Community pharmacists are also
experienced in navigating medical and prescription insurance and assisting patients who are uninsured or underinsured. Improving access to HIV screening, which occurs prior to PrEP initiation, also allows earlier HIV detection in patients who may already be infected. This can improve outcomes by allowing them to receive care sooner.

At Bell Pharmacy, Minniti said, pharmacists use telehealth to help patients understand the PrEP process, with counselors available to track their patients’ usage.

Overcoming Challenges
Across the country, some pharmacies have only recently been allowed to offer PrEP services, with guidelines varying by state, and some are finding that offering these services is not without challenges. One such challenge is ensuring standard practices are set up for proper screening and prescribing procedures. In most instances, a collaborative practice agreement with a prescriber will need to be created, which can be complex.

“Pharmacy staff also need to be appropriately trained both in the provision of PrEP from a medication standpoint and also in building strong, trusting patient relationships,” Nichols said. “It’s very important that a pharmacy doesn’t start providing PrEP without being fully trained and prepared; that could actually set back PrEP efforts.”

With increasing demands on pharmacists’ time, it can also be a challenge to stay up to date on the necessary information and literature. Another difficulty is identifying appropriate candidates for PrEP. Pharmacists also should have access to experts for questions and specific patient situations.

“Unfortunately, unconscious (or conscious) bias may play a role in the treatment of patients who request PrEP,” Nichols said. “Pharmacy staff need to be trained—and nonjudgmental—to ensure the best outcomes. Many patients who are at higher risk may already have complicated relationships or have had bad experiences with the health care system. Not all pharmacists are comfortable or experienced in talking about some of the topics that need to be discussed in detail.”

Many pharmacies are not set up to maximize patient privacy. But because conversations about PrEP can be sensitive, it’s important to have a quiet, private place for the pharmacist and the patient to have in-depth, honest discussions.

Important Discussions
For pharmacies offering PrEP services, it’s vital that patients know these are available, what they are, and why they are important. Some key discussion points between a pharmacist and a patient, Nichols noted, include the importance of adherence (as these aren’t medications that you can miss and still prevent HIV), the importance of routine HIV testing, safe sex practices, and potential adverse effects and what to do if they occur.

“It seems that pharmacists who have graduated from pharmacy school more recently feel more comfortable discussing PrEP and have had more training and education on it,” Lopez said. “Training programs are needed, particularly for pharmacists who have been in practice longer, to ensure positive outcomes.”

REFERENCES
Empowering Pharmacist-Physician Collaboration

As a pharmacist, embedding yourself in a primary care practice can have positive outcomes for both patients and your business.

By Aine Cryts
Although the number of smokers continues to fall, about 13 of every 100 US adults were smoking cigarettes in 2020 (12.5% vs 20.9% in 2005). This means that approximately 30.8 million American adults smoke cigarettes, and more than 16 million are living with smoking-related conditions.

According to Joe Moose, PharmD, a clinical pharmacist, co-owner of Mount Pleasant, North Carolina-based Moose Pharmacy, and director of strategy and luminary development with CPESN USA, smoking-cessation programs are an ideal way for independent pharmacists to collaborate with physician practices.

“What we don’t have in health care are good signals of failure,” said Moose. A primary care physician (PCP) can tell their patient to quit smoking, write prescriptions for nicotine patches and amlodipine to control their blood pressure, and ask the patient to buy a blood pressure cuff for monitoring purposes. But too often, the patient doesn’t act on their physician’s recommendations.

Cigarette smoking claims more than 480,000 American lives—approximately 1 in 5 of total US deaths—each year, according to the CDC. This makes smoking the leading cause of preventable disease, disability, and death in the United States.
“Ultimately...the primary role of the pharmacist is ensuring that medications are utilized in the safest, most effective, most efficient manner. Facilitating communication is only going to enhance that.”

TOM KALISTA, PHARM.D

The PCP’s goals include controlling their patient’s blood pressure and starting them on a smoking-cessation program. But without access to the patient’s care plan, the pharmacist doesn’t know that the PCP wants their patient to start the program and monitor their blood pressure in the first place.

At Moose Pharmacy, prescriptions will pop up for smoking-cessation patches and amlodipine, but the patient may tell Moose they are not ready to quit smoking. The conversation could end right there, the patient becoming a statistic who joins the more than 16 million Americans living with smoking-related conditions. Or the pharmacist can seize the opportunity to partner with the PCP and ensure they have access to the patient’s care plan, said Moose. The challenge is getting paid for this work. The solution, according to Moose, is what he calls a neighborhood accountable care organization (ACO).

**Embed Pharmacists in the Physician’s Practice**

The immediate impact of the pharmacist’s lack of awareness of the patient’s care plan is that the patient may pick up their amlodipine but not start the smoking-cessation program or use the cuff to monitor their blood pressure at home, said Moose.

The remedy is to embed a pharmacist in the PCP’s office for 40 hours a week to learn about patients’ care plans and reinforce and support their efforts to quit smoking, manage their diabetes, or control their blood pressure, he added. This enables the pharmacist to meet with patients directly following their visits to the practice. Immediate benefits include the opportunity for the pharmacist to learn in real time about patients’ care plans, access the practice’s electronic health record, and receive a “warm hand-off” from the clinicians at the practice as an integrated part of the patient experience, Moose explained. These connections are initially made in person at the practice between the embedded pharmacist and the clinical team. And when patients receive a follow-up call from a pharmacy technician at Moose Pharmacy, the whole process feels seamless.

This same collaborative model can be applied in the treatment of other chronic conditions, such as diabetes and hypertension. It can also help the practice successfully achieve quality measures to ensure the practice gets its full value-based care payments, Moose added.

That’s where the neighborhood ACO model comes in, explained Moose. Creating a neighborhood ACO means that accountability for patients doesn’t just rest with the PCP while the pharmacist focuses only on dispensing medications and working with the pharmacy benefit manager. Instead, both physician and pharmacist are accountable for the same measures, which can include reducing blood pressure or getting patients to stop smoking, 2 goals of the value-based model, according to Moose.

What’s missing, though, is assurances that the pharmacist is paid in addition to the PCP’s practice. Moose kicks starts compensation conversations with the practice leader after collaborating on data mining to determine missed annual wellness visits for adult patients, chronic care management opportunities, remote patient monitoring opportunities, and the number of patients with diabetes whose glycated hemoglobin A1c levels are above 9, an indication their condition is being poorly treated.

The simple question Moose poses to practice leaders is this: “If [our pharmacists] complete these things and bring in half a million dollars in payments to the practice, is that worth making a $100,000 payment to Moose Pharmacy?”

But even if Moose is successful with this pitch and delivers on the value promised to the practice, he knows his pharmacists must continue to deliver value or he risks the practice choosing to hire a nurse to take on the same work at 70% of the cost.

Moose’s advice? “You have to be valuable...and help generate income.”

Jessica Gustin, PharmD, pharmacy manager at Gwinnett Drugs in Lawrenceville, Georgia, agreed it’s important for pharmacists to show their worth to physicians. Consultations with patients experiencing chronic pain is one area in which she has achieved success. Providing this service is important because many people pass judgment on individuals taking opioids for pain management when they may actually need them, said Gustin. She is also co-founder and chief operating officer of SynerGrx, based in Chamblee, Georgia, which facilitates collaboration between pharmacists and physicians.

After asking patients about their pain management challenges, Gustin can discuss the adverse effects of opioids, provide access to naloxone HCl (Narcan), and suggest patients participate in physical therapy.

**Collaborate With Physicians on Diabetes Management**

Eklavya Lalwani, Pharm.D, pharmacist-in-charge at Olden Pharmacy in Hamilton, New Jersey, said that pharmacists—with their 6 to 8 years of education in a pharmacy school program in addition to clinical knowledge and skills—are uniquely prepared to provide clinical services. Despite this education and experience, though, pharmacists are “extremely underutilized,” he said.

Lalwani, who is also a preceptor for Fairleigh Dickinson University School
of Pharmacy and Health Sciences, said a good way to start collaborating with physician practices is to focus more closely on patients with diabetes. For example, when a patient says their insulin is too expensive, the pharmacist can call the physician and suggest the patient switch to a less expensive biosimilar with a lower co-pay. Most of the time, the pharmacist is talking to the receptionist, a medical assistant, or a nurse in these conversations. Over time, these team members start to remember the pharmacist and look to them as an expert. Lalwani also steals a page from the pharmaceutical sales rep's book by occasionally showing up for quick in-person meetings at practices.

The ever-present challenge, though, is getting paid for chronic condition management, Lalwani noted. The American Society of Health-System Pharmacists (ASHP) provides guidance to pharmacies on billing Medicare for diabetes self-management. First, the pharmacy needs to set up a diabetes self-management training/education program that has been accredited or recognized by the American Diabetes Association or Association of Diabetes Care & Education Specialists. The program can be run and managed by a registered dietitian, nurse, or pharmacist.4

For billing, the pharmacy must use the practice's or pharmacy's National Provider Identifier (NPI) rather than the pharmacist's NPI. Payment can range from $15 per patient for a group-based diabetes self-management training education session to $51 for a 30-minute session for an individual patient, according to ASHP.

**Collaboration Improves Clinical Outcomes**

“Ultimately…the primary role of the pharmacist is ensuring that medications are utilized in the safest, most effective, most efficient manner,” said Tom Kalista, PharmD, a lecturer at the University of Rhode Island College of Pharmacy. “Facilitating communication is only going to enhance that.”

Frequently, the biggest pitfalls are difficulties that occur between prescribing and dispensing, he said. Reviewing drug use and insurance coverage and addressing questions about cost and dosing concerns can take weeks, which introduces delays in patients’ receiving therapy, Kalista explained. “Any delays have an impact in terms of long-term outcomes.”

Kalista recalled a time over the Christmas holidays when a family of 5 came to the pharmacy unsure if they all had COVID-19 or strep throat. As a result of the pharmacy’s collaboration with a local physician, the family was able to access a diagnosis and treatment within 25 minutes. In addition, they were advised against going to a New Year’s Eve party to avoid spreading the strep infection.

“Picking up the phone or walking into the physician’s office is probably the biggest hurdle to [collaboration] because all the parties have the same intention, which is caring for patients,” Kalista said.

Do you have any tips for empowering collaboration in your practice? Email your comments to lbiscaldi@mjhlifesciences.com.

**REFERENCES**


Jessica Gustin, PharmD, pharmacy manager at Gwinnett Drugs in Lawrenceville, Georgia

Eklavya Lalwani, PharmD, pharmacist-in-charge at Olden Pharmacy in Hamilton, New Jersey

Joe Moose, PharmD, clinical pharmacist, co-owner of Moose Pharmacy in Mount Pleasant, North Carolina

Tom Kalista, PharmD, lecturer at the University of Rhode Island College of Pharmacy
Long COVID goes by several names: post-COVID conditions, postacute sequelae of SARS-COV-2 infection (PASC), long-haul COVID, post-acute COVID syndrome (PACS), and chronic COVID. But regardless of the term used, the exact definition and symptomology of the condition are still developing as the science unfolds.

Long COVID involves a constellation of mild to severe symptoms across body systems. According to the CDC, it consists of “new, recurring, or ongoing symptoms and clinical findings 4 or more weeks after infection, sometimes after initial symptom recovery.” Even those who have never tested positive—due to inadequate or inaccurate testing, false-negative antibody tests, or waning antibody levels—can develop long COVID, noted the agency. At present, no available laboratory tests exist to confirm the condition.

Patients of any age can develop long COVID, but it is more common in adults. According to the CDC, it consists of “new, recurring, or ongoing symptoms and clinical findings 4 or more weeks after infection, sometimes after initial symptom recovery.” Even those who have never tested positive—due to inadequate or inaccurate testing, false-negative antibody tests, or waning antibody levels—can develop long COVID, noted the agency. At present, no available laboratory tests exist to confirm the condition.

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A Review of Long COVID Symptoms

Long COVID has documented, multiorgan system effects. According to Yale Medicine, the CDC, and Britain’s National Institute for Health and Care Excellence, these symptoms include, but are not limited to, the following:

- **Cardiovascular:** Rapid or irregular heartbeat (palpitations), autonomic dysfunction such as postural orthostatic tachycardia syndrome (POTS)
- **Respiratory:** Shortness of breath, chest pain or discomfort, cough
- **Gastrointestinal:** Diarrhea, nausea and/or abdominal pain, reduced appetite
- **Neurological:** Memory loss, brain fog, loss of smell and/or taste, headache, insomnia, numbness, delirium, visual impairment, and mobility problems
- **Psychological:** Anxiety, depression, posttraumatic stress disorder
- **Dermatological:** Rashes, hair loss
- **Musculoskeletal:** Joint pain, muscle pain/weakness
- **Ear, nose, and throat:** Sore throat, earache, tinnitus, hearing loss
- **Reproductive:** Menstrual cycle changes
- **Other ongoing symptoms:** Fatigue, dizziness, intermittent low-grade fever, postexertional malaise

How Can Pharmacists Help?

Mary Ann Kliethermes, PharmD, director of medication safety and quality at the American Society of Health-System Pharmacists, shared some ways in which pharmacists can recognize long COVID in patients and assist them with managing their symptoms.

Although pharmacists do not diagnose long COVID in patients, they can help identify the condition, Kliethermes said. Pharmacists are increasingly likely to have contact with patients affected by long COVID and can use current data to identify those who may be at risk.

“Patients come to the pharmacy for help and may discuss their symptoms, seeking OTC relief for long COVID,” Kliethermes noted. She added that this is a good opportunity for pharmacists to provide counsel and recommend to patients that they visit a physician rather than attempt to treat themselves.

For long COVID management, currently, “there is no standard treatment protocol other than pulmonary and cardiac rehabilitation and the administration of supplemental oxygen,” Kliethermes told Drug Topics®. Patients may be treated for specific symptoms by a primary care physician or a specialist of the affected body system.

Pharmacists should help patients coordinate their prescriptions across specialties to prevent drug interactions, Kliethermes added. They can also coordinate with patients to evaluate what OTC drugs they are taking along with prescribed medicines, to...
prevent additional interactions and maximize effectiveness. Pharmacists can also advise patients which OTC products can help alleviate symptoms. Kliethermes emphasized that there are no proven alternative medicine treatments for long COVID, so pharmacists should ensure these substances do not interact with medically approved treatments. Finally, she advised pharmacists to keep up with developments in the literature as the science evolves by monitoring clinical trials and using research databases such as PubMed.

“**There is no standard treatment protocol [for long COVID] other than pulmonary and cardiac rehabilitation and the administration of supplemental oxygen.”**

—MARY ANN KLIETHERMES, PHARMD

**Treatment Outlook**

Other medications are being examined for their potential global effectiveness, rather than just the ability to target individual symptoms. One theory is that long COVID symptoms are caused by microclotting. One study, whose findings were recently published in *Biochemical Journal*, explored the therapeutic implications of anticoagulant use: “Consistent with this [study’s data], in a preliminary report, it has been shown that suitable and closely monitored ‘triple’ anticoagulant therapy that leads to the removal of the micro clots also removes the other [long COVID] symptoms,” the study authors wrote.1

Another possible avenue of treatment is antihistamines, with data from 2 case studies published in the *Journal for Nurse Practitioners* showing positive results for long COVID symptoms.4 The study authors noted that these data add to those of “previous studies, whose authors] have reported that patients hospitalized with COVID-19 demonstrated symptom improvement after administration of a histamine antagonist.”5 Research in these areas is still nascent, and not yet clinically approved. The biological mechanism of long COVID remains unclear. Recent studies findings published in *Frontiers in Microbiology* examined the potential causes, including injury to 1 or more organs due to acute SARS-CoV-2 infection, the virus persistently infecting specific tissues, or the reactivation of neurotrophic pathogens (such as herpesviruses), as COVID-19 dysregulates the immune system. Those investigators also noted that long COVID may be caused by SARS-CoV-2 interacting with the patient’s virome or microbiome communities or by coagulation or clotting issues, or result from dysfunctional vagus nerve or brainstem signals. Other possibilities include primed immune cell ongoing activity, and autoimmunity caused by “molecular mimicry between pathogen and host proteins.”6 Because of the wide range of potential causes, the authors emphasized that the individualized array of symptoms in each patient will require different approaches to offer the best care.

While the science develops, pharmacists can help patients manage this mysterious and often debilitating condition. Pharmacists and providers can follow the CDC’s interim guidance on evaluating and caring for patients with long COVID.

“Understanding of post-COVID conditions remains incomplete and guidance for healthcare professionals will likely change over time as the evidence evolves,” the CDC wrote.7 It is essential to afford practicing pharmacists the time and access to resources and professional development to keep up with emerging research, so they are prepared to identify patients with long COVID and assist them with symptom management and recovery.

For references, visit drugtopics.com.

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**Who’s at Risk?**

Investigators of a recent study evaluated the risks for long COVID. Their research findings, published in *The Journal of Infectious Diseases,* included the following data:

**HIGHEST RATES OF LONG COVID**

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**THE PREVALENCE OF LONG COVID IN PATIENTS IN A 120 DAY SPAN**

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A n all-star slate of speakers and panelists from across the community and independent pharmacy space came together virtually on April 30 as Drug Topics® and Total Pharmacy® held the first Total Pharmacy Solutions Summit of 2022.

Keynote Address
Steven F. Moore, PharmD, vice president of Condo Pharmacy in Plattsburgh, New York, and a Community Pharmacy Enhanced Services Network (CPESN) Luminary, kicked off the day with his keynote address. Moore shared some of the strategies Condo Pharmacy has implemented to expand their point-of-care testing capabilities during the COVID-19 pandemic.

“When we started hearing about COVID-19 [about] 2 and a half years ago, one of the things we were concerned about at the pharmacy was, how do we keep the pharmacy open? What is it we can do to continue to be here for our patients?” Moore and his staff turned to point-of-care testing, which would include COVID-19 rapid antigen tests—a value to the community and to the Condo Pharmacy staff, who couldn’t afford to wait days for laboratory test results.

“Here in New York, we started working through CPESN New York… with the state of New York because, believe it or not, prior to COVID-19, pharmacists didn’t necessarily have the scope of practice rights to do [Clinical Laboratory Improvement Amendments]-waived testing,” he said. “It wasn’t part of our scope…but we quickly realized, ‘Hey, we have 5500 community pharmacies here in New York, and we need to test people.’”

“Thankfully, the governor did recognize that and moved to remove some of those barriers and obstacles that we had to testing, so we could start to do that,” he added.

Expanding on Point-of-Care Testing
Paige Clark, RPh, vice president of pharmacy programs and policy at Prescriptive Health, further expanded on the importance of, and trends in, point-of-care testing.

“Prescriptive is all about being your
To take advantage of a special offer for Drug Topics readers, call 877-854-9335 or visit www.rxsafe.com/drugtopics.
partner to provide...that connection to patients. It’s imperative that we continue to move quickly in this space; we can’t stand back and watch. We have to capture this space,” she said.

Clark also touched on scope of practice expansion for pharmacists, citing the Biden administration’s Test to Treat program, announced on March 1, 2022, as an example of scope of practice expansion. “Is [the program] perfect today? It is not. But I think what that signals to us is an enormous recognition on the part of the federal government, and entities within the federal government, that our community pharmacies are absolutely an essential access point for public health across this nation,” she said.

Employee Retention
Lisa Faast, PharmD, founder and CEO of DiversifyRx, the Pharmacy Profit Summit, and Pharmacy Badass University, was next to take the stage, with a presentation on attracting and retaining employees in today’s job market.

“As pharmacy owners...we’d love to offer our employees unlimited benefits and unlimited salaries, but unfortunately, we live in the real world where things are restricted,” Faast said. “You have to be able to adjust the benefits—and these benefits are in your control.”

These benefits, she explained, include things like salary commissions, bonuses, paid time off, insurance, scheduling, title and position, and other perks. These benefits are things that pharmacy owners can control, and need not be offered all at once. “Not all employees care about the same benefits,” she said. “If one goes up—say you increase the hourly rate—maybe another one comes down to adjust for that.”

Closing Roundtable
The day concluded with a roundtable discussion, moderated by Mohamed A. Jalloh, PharmD, BCPS, assistant professor in the clinical sciences department at Touro University California College of Pharmacy in Vallejo and Drug Topics® Editorial Advisory Board member. Jalloh was joined by Bill Holmes, MBA, CEO of RxSafe; Kevin Russell, RPh, MBA, BCACP, director of pharmacy for clinical operations at Prescriptive Health; and Moore, who returned to join the panel discussion.

“We’ve seen that the COVID-19 pandemic highlighted how important pharmacists can be with point-of-care testing,” said Jalloh. “To my panelists, my first question is, how do you envision the future of pharmacy, specifically in the context of point-of-care testing, after COVID-19?”

“We have to protect the existence of independent retail pharmacies,” said Holmes. “Ninety-five percent of people...are within 5 minutes of one of these stores. If they go away, there would be a devastating effect. Just imagine COVID-19 without independent retail pharmacies. We have to work together; we have to use these new ideas to create improved economic health of independent pharmacies.”

To watch the videos from the Total Pharmacy Solutions Summit, visit totalpharmacy.com or scan the QR code.

More than 300 attendees registered for the Total Pharmacy Solutions Summit in April. If you missed out on this day of education and insight into the community and independent pharmacy space, don’t miss our next virtual summit, taking place this fall.

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New customers find your pharmacy when searching for prescriptions on myRx.io, our patient-friendly platform for mobile devices.

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Get started with myRx Pricing today!
Ask any patient with type 1 diabetes (T1D) about disease management, and you’ll likely hear stories of meticulous monitoring, hardware challenges, and more. So it’s no surprise that enterprising patients and caregivers have begun to hack their insulin pumps and continuous glucose monitors (CGMs) to create hybrid, closed-loop automated insulin delivery (AID) systems using off-the-shelf hardware and do-it-yourself (DIY), open-source smartphone apps to build their own bionic pancreas.

Aaron J. Kowalski, PhD, CEO of the Juvenile Diabetes Research Foundation (JDRF), received a diagnosis of T1D at age 13. When he learned about the DIY closed-loop AID system called Loop, he jumped right in. “I was a very early adopter because my first responsibility is to my health and my family. I had worked in the science for many years, and I felt that the risk was worth taking,” Kowalski said.

Kowalski isn’t alone. Many JDRF staffers have T1D, and they often use open-source DIY AID systems. The same is true at Integrated Diabetes Services. Owner and clinical director Gary Scheiner, MS, CDCES, and many of his staff clinicians use open-source AID.

“I wouldn’t consider myself tech savvy; I’m tech comfortable,” Scheiner said. “DIY is not much different conceptually from what’s available commercially today, but DIY systems like Loop are more flexible (and) more customizable. Commercially available systems have serious guardrails (and) very few variables that the user can adjust, which limits functionality. With something like Loop, you can achieve higher time in range, tighter averages, and lower [hemoglobin A1c] levels than with commercially available systems because you can adjust to your daily needs more easily.”

How It Started
Insulin pumps and CGMs have been a staple in T1D care since the 1980s and early 2000s, respectively. But for a time, the 2 devices could not communicate, as no feedback loop existed between CGMs and insulin pumps to automatically regulate insulin dosing and blood glucose levels.

In 2014, some insulin pump users realized that a security flaw in the now-discontinued Medtronic pump models let them hack their pumps. Anyone with the right tech savvy could create their own algorithm, load it on a smartphone, and use real-time CGM data to calculate insulin dosing and control their pump. And thus looping—closing the CGM-insulin pump loop using DIY, open-source software—was born.

Many early adopters were parents of children with T1D who wanted to be able to remotely monitor their child’s serum glucose and adjust insulin dosing as needed, Kowalski explained. Under the banner #WeAreNotWaiting, parents formed an online community, Nightscout, an “open-source DIY project that allows real time access to CGM data,” he said. In its first iteration, Nightscout was specifically made to remotely monitor Dexcom G4 CGM data. Eager users shared Open Artificial Pancreas System (OpenAPS) documentation, including open-source reference designs, safety information, and step-by-step implementation instructions. Everything was designed to use existing FDA-approved devices, commodity hardware, and open-source software. As the information spread, AndroidAPS (for Android devices) and Loop (for iPhones and later iOS devices) focused on users in device-specific communities.

By 2016, OpenAPS users were presenting data at scientific gatherings sponsored by the American Diabetes Association and other medical organizations focused on diabetes research and care. Tidepool added Loop data in 2018 and began...
developing a commercial algorithm with financial support from JDRF and other sources. In 2021, Tidepool completed the first open-source AID algorithm 510(k) application to the FDA. Tidepool forked the original DIY Loop to create a more efficient, easier-to-use, and better documented app for the FDA submission, said Christopher Snider, Tidepool’s community and clinic success manager. DIY loopers have incorporated some of the updates, but Tidepool remains a distinct algorithm.

“We put a tight code base on the app and used human factors approaches to increase the safety and efficacy of the algorithm and improve the overall user experience,” Snider said. “When Tidepool becomes commercially available, we will have a support team in place to work with [individuals] directly, just as you would expect with any other insulin delivery system. Support is a little more nebulous in the DIY space where you go to Facebook or Twitter with questions.”

Keep Pharmacists in the Loop

In the medical device world, customer support is generally device specific; every pump, CGM, and hybrid closed-loop system has its own support team. Open source, though, lets users mix and match pumps and CGMs from different manufacturers, creating more flexibility and more choices in features.

“Insulin is prescribed as usual and the health care team still needs to figure out how much insulin the patient is using,” said Diana Isaacs, PharmD, BCPS, BCACP, BC-ADM, CDSES, endocrine clinical pharmacy specialist and remote monitoring program coordinator at the Cleveland Clinic Endocrinology and Metabolism Institute in Ohio. “With systems like Tidepool and Nightscout, we can view all the user data to figure insulin needs.”

She added, “I can’t configure a DIY system because it’s not FDA approved. But what I can do as a pharmacist is review patients’ data and advise them on ways to remain safe. We have a professional responsibility to support our patients and keep them safe.”

Although Isaacs sees open-source AID due to her location and her high visibility within the diabetes community, data published in a recent international consensus statement in Lancet Diabetes and Endocrinology estimated that approximately 10,000 individuals with diabetes are using DIY AID—a miniscule figure considering the 9 million individuals worldwide who have T1D.

John Beckner, RPh, senior director of strategic initiatives at the National Community Pharmacy Association, said that for now DIY is “just not that prevalent. And as technology continues to advance, there isn’t going to be much need to do it.”

The future of DIY will depend largely on industry. Dexcom, Medtronic, Tandem, Insulet, and other manufacturers regularly iterate existing products, bringing new systems online. And for now these products remain a closed ecosystem. “The tendency in industry is to want it all under your own shop,” Kowalski said. “If we fast forward 5 years, it would be shocking to me if we are not plugging and playing most of these components. We don’t have plug-and-play systems in the United States but we do in Europe.”

European regulators approved CamAPS FX, an Android app created by CamDiab, a JDRF-funded project at Cambridge University, in 2020. The app, which links pumps and CGMs across manufacturers, is approved for systems used by patients 1 year and older.

Kowalski predicted a future with fully interoperable closed-loop systems that combine pump X, sensor Y, and app Z. If industry doesn’t do it, DIYers will do it for them. “I was just talking with some of our team about when the Omnipod system is going to launch,” he said. “They’ve been saying publicly this fall, but in the meantime, there are a lot of [individuals] doing Omnipod DIY. If there is a tool to help diabetes be easier to manage with better numbers, that’s a first consideration.”

For references, visit drugtopics.com.
Individuals who identify as a member of the LGBTQ+ community—lesbian, gay, bisexual, transgender, and questioning/queer—face significant health care disparities and have higher risks for depression and suicide compared with other individuals.1 Pharmacists and health care providers across the spectrum must be aware of the needs of this patient population, from which terminology to use to the health care inequalities patients face.

Pharmacy owners looking to create a comfortable environment for LGBTQ+ individuals to pick up prescriptions or obtain counseling, begin by assessing pharmacists and their staff, said Alex R. Mills, PharmD, BCACP, an assistant professor of pharmacy practice (HIV, LGBTQ+ Health) at the University of Mississippi School of Pharmacy in Jackson.

“There are opportunities for cultural humility. Assess pharmacists and their staff on their understanding of the LGBTQ+ community. Are they even aware of the challenges that are happening?” Mills told Drug Topics®. “That’s the first place to start. Then identify the resources or training they need.”

Next, evaluate the physical environment. “Can you provide an affirming environment? Is there an opportunity for your [electronic medical records] system to include pronouns?” One big challenge Mills has seen at community pharmacies is the difficulties LGBTQ+ patients face in getting their prescription if their legal name is different from their affirmed name. Take, for example, a transgender patient whose legal name was John but is now Jennifer. Their insurance may still list their legal name as John, Mills explained. “Running the prescription through insurance, that name [John] will print on their prescription packaging. Is there a way to develop systems to capture the name needed to run through insurance but the end product prints the person’s name they are using now?” he asked.

The LGBTQ+ community already faces health care disparities related to insurance and health care visits. According to the 2015 US Transgender Survey,2 25% of respondents had experienced a problem with their insurance in the past year related to being transgender, such as being denied coverage for care related to gender transition or being denied coverage for routine care. Additionally, 33% of respondents who saw a health care provider in the past year reported having at least 1 negative experience related to being transgender, including being refused treatment, verbally harassed, or physically or sexually assaulted, or having to teach the provider about transgender people to obtain appropriate care, said Mills and Kyle Melin, PharmD, MSc, BCPS, during an American Society of Health-Systems Pharmacists webinar.3 Melin is an associate professor at the University of Puerto Rico School of Pharmacy in San Juan.

Sexual and gender minorities are disproportionately affected by poverty, housing instability, and discrimination within the health care system, as well as by stigma, Mills and Melin noted. “These differences in social determinants of health can lead to health disparities and poorer health outcomes,” they added.

“Embracing the diversity of all patients and understanding where patients come from is going to affect the ability to provide good care,” Mills said. Not every patient who comes into the pharmacy to pick up their medications has had a good experience with the health care system. “That is what is preventing them from being engaged in their care. It’s recognizing that we need to paint that patient in a different picture and appreciate how the intersectionality between sexual orientation and/or gender identity affects one’s health care experience, so we can provide a holistic, person-centered approach to their health.”

Being comfortable with basic terminology used by sexual and gender minorities goes a long way toward creating a welcoming and affirming environment for LGBTQ+ patients. Some of the most important terms to know are transgender woman, someone assigned male at birth who identifies as a woman, and transgender man, someone assigned female at birth who identifies as a man.

It’s also important to understand that queer can be used by someone who doesn’t identify under just one aspect of the LGBTQ+ umbrella, and to be mindful that some individuals find this term offensive, according to Mills. Instead, allow individuals to self-dis-
close the term, rather than assigning it to them.
Pharmacists should also be wary of deadnaming—identifying a patient by the wrong name—or misgendering someone by using the wrong pronoun, Mills advised. Patients may even see the error themselves when they log into patient portals. “Those who are charting should know that it is very dysphoric for patients who may be using a different name, and be mindful of this during the documentation process” Mills noted.

“Stop making assumptions about people,” Mills advised. “If you make assumptions that they identify as a transgender male, for example, and assume they are romantically attracted to females, you may miss an opportunity to discuss with a high-risk patient the benefits of taking HIV pre-exposure prophylaxis [PrEP]. Essentially, sexual orientation and gender identity can be independent of each other.”

Do you have any tips for creating a welcoming and inclusive space for your LGBTQ+ patients? Email your comments to lbiscaldi@mjhlifesciences.com.

REFERENCES

Creating an Inclusive Pharmacy

In a 2016 resource guide, the Human Rights Campaign outlines 5 steps that pharmacists can take to create an inclusive, comfortable pharmacy environment:

- **Provide staff training on LGBTQ+ culturally affirming care.** This should include information on LGBTQ+ identities, terminology, and health disparities, as well as best practices for avoiding making stereotypes and assumptions about sexual orientation and gender identity.

- **Create a welcoming physical environment.** LGBTQ+ patients report searching for subtle clues to determine if an environment is accepting. To signal that the pharmacy is an accepting environment, consider displaying a rainbow sticker; ensuring that educational and marketing materials display same-sex couples or families; and displaying LGBTQ+-specific education, materials, and resources.

- **Develop a clear restroom policy.** Ensure that customers have access to a restroom that matches their gender identity.

- **Communicate correctly.** Use the right words when communicating, verbally and on pharmacy forms. Avoid assumptions, use gender-neutral language if unsure of pronouns, and allow patients to indicate their pronouns on intake forms.

- **Reach out and engage.** Engaging with the LGBTQ+ community goes a long way toward creating an inclusive, welcoming environment. Consider hosting community events with local LGBTQ+ organizations or recognize and celebrate events such as LGBT Health Week.
Indications and Usage

VAXNEUVANCE is indicated for active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F in adults 18 years of age and older.

**VAXNEUVANCE delivered robust immunogenicity against key disease-causing *Streptococcus pneumoniae* serotypes**

A strong immune response to 15 serotypes, including noninferior immune responses for the 13 serotypes shared with PCV13

**Study Design:** Double-blind, active comparator-controlled study in which pneumococcal vaccine-naïve participants 50 years of age and older were randomized to receive either VAXNEUVANCE (N=604) or PCV13 (N=601).

VAXNEUVANCE also elicited superior immune responses for 2 unique serotypes, 22F and 33F, vs PCV13.

**Select Safety Information**

Do not administer VAXNEUVANCE to individuals with a severe allergic reaction (eg, anaphylaxis) to any component of VAXNEUVANCE or to diphtheria toxoid.

Some individuals with altered immunocompetence, including those receiving immunosuppressive therapy, may have a reduced immune response to VAXNEUVANCE.

The most commonly reported solicited adverse reactions in individuals 18 through 49 years of age were: injection-site pain (75.8%), fatigue (34.3%), myalgia (28.8%), headache (26.5%), injection-site swelling (21.7%), injection-site erythema (15.1%), and arthralgia (12.7%).
Select Safety Information (continued)

The most commonly reported solicited adverse reactions in individuals 50 years of age and older were: injection-site pain (66.8%), myalgia (26.9%), fatigue (21.5%), headache (18.9%), injection-site swelling (15.4%), injection-site erythema (10.9%), and arthralgia (7.7%). Vaccination with VAXNEUVANCE may not protect all vaccine recipients.

Superior immune response vs PCV13 against serotype 3—the leading cause of IPD in the US­¹

VAXNEUVANCE elicited

62% HIGHER IMMUNOGENICITY¹,a

than PCV13 against serotype 3

⁰GMT ratio vs PCV13: 1.62 (95% CI: 1.40-1.87).

Randomized controlled trials assessing the clinical efficacy of VAXNEUVANCE compared to PCV13 have not been conducted.

Serotype-specific comparative OPA GMTs for serotype 3

VAXNEUVANCE PCV13

0 50 100 150 200 250 GMT

CI, confidence interval; GMT, geometric mean titer; OPA, opsonophagocytic activity.

VAXNEUVANCE is an option for pneumococcal vaccination in a broad range of patients at increased risk, including older adults, adults with chronic medical conditions or behavioral risk factors, and certain immunocompromised adults.⁰

⁰For example, adults aged 65 years or older; those with diabetes, chronic heart disease, chronic lung disease, or chronic liver disease; smokers or those with alcoholism; or adults living with HIV.

Take every opportunity to help protect appropriate adults in your pharmacy at increased risk for IPD.

Please read the adjacent Brief Summary of the Prescribing Information.

Reference:

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Brief Summary of the Prescribing Information for VAXNEUVANCE

DOSAGE AND ADMINISTRATION

For intramuscular use only.

Dosage: Administer a single 0.5 mL dose.

Administration: Hold the prefilled syringe horizontally and shake vigorously immediately prior to use to obtain an opalescent suspension in the prefilled syringe. Do not use the vaccine if it cannot be resuspended. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use if particulate matter or discoloration is observed.

CONTRAINdications

Do not administer VAXNEUVANCE to individuals with a severe allergic reaction (e.g., anaphylaxis) to any component of VAXNEUVANCE or to diphtheria toxoid.

WARNINGS AND PRECAUTIONS

Altered Immunocompetence: Some individuals with altered immunocompetence, including those receiving immunosuppressive therapy, may have a reduced immune response to VAXNEUVANCE.

ADVERSE REACTIONS

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

The most commonly reported solicited adverse reactions in individuals 18 through 49 years of age were: injection-site pain (75.8%), injection-site swelling (34.3%), myalgia (28.8%), headache (26.5%), injection-site erythema (21.7%), injection-site edema (15.1%), and arthralgia (12.7%). The most commonly reported solicited adverse reactions in individuals 50 years of age and older were: injection-site pain (66.8%), myalgia (26.9%), fatigue (21.5%), headache (18.9%), injection-site swelling (15.4%), injection-site erythema (10.9%), and arthralgia (7.7%).

Safety Assessment: Clinical Studies:

The safety of VAXNEUVANCE was assessed in 7 randomized, double-blind clinical studies conducted in the Americas, Europe, and Asia Pacific, in which 5,630 adults 18 years of age and older received VAXNEUVANCE and 1,808 adults received Prevnar 13 (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM, Protein]). In Studies 1-3 (NCT03950262, NCT03950286, and NCT03480763), a total of 3,032 adults 50 years of age and older with no history of pneumococcal vaccination received VAXNEUVANCE and 1,154 participants received Prevnar 13. In Study 4 (NCT03547167), adults 18 through 49 years of age with no history of pneumococcal vaccination, including individuals with increased risk of developing pneumococcal disease, received VAXNEUVANCE and 1,154 participants received Prevnar 13, followed by PNEUMOVAX 23 six months later. In Study 5 (NCT02573181), adults 65 years of age and older previously vaccinated with PNEUMOVAX 23 (at least 1 year prior to study entry) received VAXNEUVANCE (N=127) or Prevnar 13 (N=126). In Study 6 (NCT03615482), adults 50 years of age and older received VAXNEUVANCE concomitantly with a seasonal inactivated quadrivalent influenza vaccine (Fluarix Quadrivalent; GIV (Group 1, N=600) or nonconcomitantly 30 days after GIV (Group 2, N=585). In this study population, 20.9% of individuals had a history of prior vaccination with PNEUMOVAX 23. In Study 7 (NCT03480802), HIV-infected adults 18 years of age and older received VAXNEUVANCE (N=152) or Prevnar 13 (N=150), followed by PNEUMOVAX 23 two months later.

The clinical studies included adults with stable underlying medical conditions (e.g., diabetes mellitus, renal disorders, chronic heart disease, chronic liver disease, chronic lung disease including asthma) and/or behavioral risk factors (e.g., smoking, increased alcohol use) that are known to increase the risk of pneumococcal disease. Overall, the mean age of the participants was 58 years and 54.6% were female. The racial distribution was as follows: 72.3% were White, 9.9% were Asian, 8.1% were American Indian or Alaska Native, 7.4% were Black or African American, and 18.1% were of Hispanic or Latino ethnicity.

In all studies, safety was monitored using a Vaccination Report Card (VRC) for up to 14 days postvaccination. Study investigators reviewed the VRC with the participants 15 days postvaccination to ensure consistency with protocol definitions. The analyses presented in Tables 1-3 below reflect the information based on the final assessment by the study investigators. Oral bone temperature and injection-site adverse reactions were solicited on Day 1 through Day 5 postvaccination. Systemic adverse reactions were solicited on Day 1 through Day 14 post vaccination. Unreported adverse events were reported on Day 1 through Day 14 post vaccination.

The duration of the safety follow-up period for serious adverse events postvaccination with VAXNEUVANCE was 1 month in Study 5; 2 months in Study 7; 6 months in Studies 1, 2, 4, and 6; and 12 months in Study 3.

Solicited Adverse Reactions

The percentage of participants with solicited adverse reactions that occurred within 5 or 14 days following administration of VAXNEUVANCE or Prevnar 13 in 3 studies are shown in Tables 1-3. The majority of solicited adverse reactions lasted <3 days.

Table 1: Percentage of Participants with Solicited Local and Systemic Adverse Reactions in Pneumococcal Vaccine-Naïve Adults 50 Years of Age and Older (Study 2)*

<table>
<thead>
<tr>
<th>Local Reactions*</th>
<th>VAXNEUVANCE (%) N=1,134</th>
<th>Prevnar 13 (%) N=378</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>66.8</td>
<td>52.2</td>
</tr>
<tr>
<td>Grade 3†</td>
<td>0.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Erythema</td>
<td>10.9</td>
<td>9.6</td>
</tr>
<tr>
<td>Any &gt;10 cm</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Swelling</td>
<td>15.4</td>
<td>14.3</td>
</tr>
<tr>
<td>Any &gt;10 cm</td>
<td>0.2</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Study 2 (NCT03950286) was a randomized (1:1), double-blind, active comparator-controlled, lot to lot consistency study. Safety was monitored using a Vaccination Report Card (VRC) for up to 14 days postvaccination. The table represents the final assessment by the study investigators upon review of the VRC 15 days post vaccination, to ensure consistency with protocol definitions.

†Solicited on Day 1 through Day 5 postvaccination

‡Any use of narcotic pain reliever or prevents daily activity

§Solicited on Day 1 through Day 14 postvaccination

¶Percentages are based on the number of participants with temperature data

N=Number of participants vaccinated

Table 2: Percentage of Participants with Solicited Local and Systemic Adverse Reactions in Pneumococcal Vaccine-Naïve Adults 18 to 49 Years of Age With or Without Risk Factors for Pneumococcal Disease (Study 4)*

<table>
<thead>
<tr>
<th>Systemic Reactions§</th>
<th>VAXNEUVANCE (%) N=1,134</th>
<th>Prevnar 13 (%) N=378</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>21.5</td>
<td>22.2</td>
</tr>
<tr>
<td>Grade 3†</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Headache</td>
<td>18.9</td>
<td>18.7</td>
</tr>
<tr>
<td>Grade 3†</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>26.9</td>
<td>21.7</td>
</tr>
<tr>
<td>Grade 3†</td>
<td>0.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Grade 3†</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Fever‡</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Study 4 (NCT03547167) was a randomized (1:1), double-blind, active comparator-controlled, lot to lot consistency study. Safety was monitored using a Vaccination Report Card (VRC) for up to 14 days postvaccination. The table represents the final assessment by the study investigators upon review of the VRC 15 days post vaccination, to ensure consistency with protocol definitions.

†Solicited on Day 1 through Day 5 postvaccination

‡Any use of narcotic pain reliever or prevents daily activity

§Solicited on Day 1 through Day 14 postvaccination

¶Percentages are based on the number of participants with temperature data

N=Number of participants vaccinated

PATIENT COUNSELING INFORMATION

• Inform the patient that vaccination with VAXNEUVANCE may not protect all vaccine recipients.

• Discuss the following with the patient:

  - The possible side effects of the vaccine or vaccine ingredients.
  - The benefits and risks of the vaccine.
  - The importance of vaccination to prevent pneumococcal disease.
  - The importance of reporting any adverse events to the healthcare provider.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Developmental toxicity studies have been performed in female rats. In these studies, female rats received a human dose of VAXNEUVANCE by intramuscular injection on gestation days 6 through 15 and once during lactation. These studies revealed no evidence of harm to the fetus due to VAXNEUVANCE.

Overall, there were no clinically meaningful differences in the safety profile or response to VAXNEUVANCE when administered with or without inactivated quadrivalent influenza vaccine. The safety profile was similar when VAXNEUVANCE was administered with or without inactivated quadrivalent influenza vaccine.

The safety profile was similar when VAXNEUVANCE was administered with or without inactivated quadrivalent influenza vaccine.

The safety profile was similar when VAXNEUVANCE was administered with or without inactivated quadrivalent influenza vaccine.

The safety profile was similar when VAXNEUVANCE was administered with or without inactivated quadrivalent influenza vaccine.

The safety profile was similar when VAXNEUVANCE was administered with or without inactivated quadrivalent influenza vaccine.

The safety profile was similar when VAXNEUVANCE was administered with or without inactivated quadrivalent influenza vaccine.
**PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Discuss the following with the patient:

- Provide the required vaccine information to the patient.
- Inform the patient of the benefits and risks associated with vaccination.
- Inform the patient that vaccination with VAXNEUVANCE may not protect all vaccine recipients.
- Instruct the patient to report any serious adverse reactions to their healthcare provider who in turn should report such events to the vaccine manufacturer or the U.S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7976, or report online at www.vaers.hhs.gov.

For more detailed information, please read the Prescribing Information.

Useful links:
- NCT03615482
- NCT02573181
- NCT03950622
- NCT03950856
- NCT03480763

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**Table 3: Percentage of Participants with Solicited Local and Systemic Adverse Reactions in Adults 65 Years of Age and Older with Previous Pneumococcal Vaccination (Study 5)*

<table>
<thead>
<tr>
<th>Reaction</th>
<th>VAXNEUVANCE (%)</th>
<th>Prevnar 13 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=127</td>
<td>N=126</td>
</tr>
</tbody>
</table>

Local Reactions‡

<table>
<thead>
<tr>
<th>Reaction</th>
<th>VAXNEUVANCE (%)</th>
<th>Prevnar 13 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>55.1</td>
<td>44.4</td>
</tr>
<tr>
<td>Grade 3‡</td>
<td>0.8</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Systemic Reactions§

<table>
<thead>
<tr>
<th>Reaction</th>
<th>VAXNEUVANCE (%)</th>
<th>Prevnar 13 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>18.1</td>
<td>19.0</td>
</tr>
<tr>
<td>Grade 3‡</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Headache</td>
<td>13.4</td>
<td>15.9</td>
</tr>
<tr>
<td>Grade 3‡</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15.7</td>
<td>11.1</td>
</tr>
<tr>
<td>Grade 3‡</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5.5</td>
<td>8.7</td>
</tr>
<tr>
<td>Grade 3‡</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Unsolicited Adverse Reactions

Across all studies, injection-site pruritus was reported to occur in up to 2.8% of adults vaccinated with VAXNEUVANCE.

Serious Adverse Events

Across all studies, among participants 18 years of age and older who received VAXNEUVANCE (excluding those who received QIV concomitantly, N=5,030) or Prevnar 13 (N=4,808), serious adverse events within 30 days postvaccination were reported by 0.4% of VAXNEUVANCE recipients and by 0.7% of Prevnar 13 recipients. In a subset of these studies, among those who received VAXNEUVANCE (N=4,751) and Prevnar 13 (N=1,532), serious adverse events within 6 months postvaccination were reported by 2.5% of VAXNEUVANCE recipients and by 2.4% of Prevnar 13 recipients.

There were no notable patterns or numerical imbalances between vaccination groups for specific categories of serious adverse events that would suggest a causal relationship to VAXNEUVANCE.

Developmental toxicity studies have been performed in female rats administered a human dose of VAXNEUVANCE on four occasions, twice prior to mating, once during gestation and once during lactation. These studies revealed no evidence of harm to the fetus due to VAXNEUVANCE.

Data

**Animal Data**

Developmental toxicity studies have been performed in female rats. In these studies, female rats received a human dose of VAXNEUVANCE by intramuscular injection on day 28 and day 7 prior to mating, and on gestation day 6 and on lactation day 7. No vaccine related fetal malformations or variations were observed. No adverse effect on pup weight up to post-natal day 21 was noted.

**Lactation**

**Risk Summary**

Human data are not available to assess the impact of VAXNEUVANCE on milk production, its presence in breast milk, or its effects on the breastfed child. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for VAXNEUVANCE and any potential adverse effects on the breastfed child from VAXNEUVANCE or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

**Pediatric Use**

The safety and effectiveness of VAXNEUVANCE in individuals younger than 18 years of age have not been established.

**Geriatric Use**

Of the 4,389 individuals aged 50 years and older who received VAXNEUVANCE, 2,478 (56.5%) were 65 years and older, and 479 (10.9%) were 75 years and older. Overall, there were no clinically meaningful differences in the safety profile or immune responses observed in older individuals (65 to 74 years and 75 years of age and older) when compared to younger individuals.

**Individuals at Increased Risk for Pneumococcal Disease**

**Adults with HIV Infection**

In a double-blind, descriptive study (Study 7), the safety and immunogenicity of VAXNEUVANCE were evaluated in pneumococcal vaccine-naïve HIV-infected adults 18 years of age and older, with CD4+ T-cell count ≥50 cells per microliter and plasma HIV RNA value <50,000 copies/mL. Participants were randomized to receive VAXNEUVANCE (N=152) or Prevnar 13 (N=150), followed by PNEUMOVAX 23 two months later. Anti-pneumococcal opsonophagocytic activity (OPA) geometric mean antibody titers (GMTs) were higher after administration of VAXNEUVANCE, compared to pre-vaccination, for the 15 serotypes contained in VAXNEUVANCE. After sequential administration with PNEUMOVAX 23, OPA GMTs observed at 30 days after PNEUMOVAX 23 vaccination were numerically similar between the two vaccination groups for all 15 serotypes contained in VAXNEUVANCE. The safety profile of VAXNEUVANCE was similar between the two vaccination groups. The effectiveness of VAXNEUVANCE in HIV-infected individuals has not been evaluated.

**NONCLINICAL TOXICOLOGY**

Carcinogenesis, Mutagenesis, Impairment of Fertility

VAXNEUVANCE has not been evaluated for carcinogenic or mutagenic potential or for impairment of male fertility in animals. VAXNEUVANCE administered to female rats had no effect on fertility.

**PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Discuss the following with the patient:

- Provide the required vaccine information to the patient.
- Inform the patient of the benefits and risks associated with vaccination.
- Inform the patient that vaccination with VAXNEUVANCE may not protect all vaccine recipients.
- Instruct the patient to report any serious adverse reactions to their healthcare provider who in turn should report such events to the vaccine manufacturer or the U.S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7976, or report online at www.vaers.hhs.gov.

For more detailed information, please read the Prescribing Information.

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A Lesson From the Friendly Skies

A twice-cancelled trip, a delayed flight, and a United Airlines employee can show retail pharmacies how it's done.

The COVID-19 pandemic and immunization seems to be winding down for us in the community pharmacy space. As I’ve seen over the past 41 years of pharmacy practice, we will not take time to celebrate victory but will move on to the next crisis. Crisis management is how we seem to operate.

I remember back in the 1980s when the battle was for more than average wholesale price plus $2.55 reimbursement. In the 1990s the battle was with drug utilization review and the HIPAA, and although many independent pharmacies closed during that time, we still survived.

Independent pharmacies are still surviving thanks to those hard-nosed businesspeople/pharmacists who work relentlessly to keep out of the jaws of the major chains; sometimes we feel like guppies in a tank of piranhas. But in spite of those outside influences, we take care of every individual patient who reaches out to us for our expertise and help.

I’m typing this column as I sit in Pittsburgh International Airport. My amazing wife of 41 years planned this trip 3 years ago. Our trip has been canceled twice, but we are now ready to fly to Washington, DC, connect in Frankfurt, Germany, and then jet off to Prague. Denise, my wife, has been vigilant in following all the recommendations. Yesterday we spent the morning at an independent pharmacy, Perry Drug Store in Perryopolis, Pennsylvania—the only place within 100 miles of us that performed immediate PCR tests.

Our results were negative. Our luggage was checked in. We brought our own lunch and arrived 3 hours early... and we just got a text saying our flight from Pittsburgh to Washington has been delayed by 1 hour. We will miss our flight to Frankfurt. Tough luck, go figure it out is the vibe I’m getting as I sit here at gate A-4.

Daniel, a young United Airlines employee, has wheeled over a snack cart and is assisting passengers. He gives Denise word that he has everything taken care of. We will still arrive in Washington on the same flight, still 1 hour late, but Daniel has made arrangements for us to take a different flight—this one on a different airline—to Germany. Taking care of customers who have spent years preparing for this vacation is his first priority, even if it means steering business to a rival airline.

United Airlines has taken a beating over the years regarding their customer service. In 2009, singer-songwriter Dave Carroll released “United Breaks Guitars,” a song that went viral and dropped the value of their stock 10% in a matter of 1 week. In 2017, the airline took another hit when reports emerged of their forcible removal of a passenger from a flight due to overbooking.

Since then, United has responded positively to an outpouring of negative publicity. My personal experience with the company was also a positive one. Daniel didn’t say, “It’s not my problem,” or “I’m not the guy who made the plane an hour late.” He didn’t say, “It isn’t my job;” instead, he took care of the people standing in front of him. We pharmacists do the same thing to serve our patients: We spend hours on the phone with insurance companies who create problems for us to solve.

The big 4 pharmacy chains have also taken a hit, at least on social media, and pharmacists are leaving in droves. Frequently these posts show signs stating the pharmacy is “closed for business due to lack of staffing.” Will the pharmacists and pharmacy employees be the ones to bring these big 4—who routinely understaff and provide unpleasant working conditions—to their knees?

United Airlines learned a valuable lesson and has trained their employees to take care of the people in front of them. Pharmacists at the big 4 want to do the same. But working conditions in these pharmacies are miserable at best, and pharmacists are quitting in droves. Anytime you see a pharmacist counting pills, answering an unscreened phone call, or ringing a cash register, it is a failure. The big 4, and many others, continue to fail. Pay attention to what United does: Take care of your employees and they will take care of your patients.

Peter A. Kreckel, RPh, practices community pharmacy in Altoona, Pennsylvania.

For references, visit drugtopics.com
Daridorexant Receives Approval for Insomnia Treatment

Daridorexant demonstrated significant reduction in daytime sleepiness among other measures  

**Efficacy**

Two multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 3 trials (study 1, NCT03545191; study 2, NCT03575104) evaluated efficacy. Investigators randomly assigned 1854 patients to receive daridorexant or placebo once in the evening for 3 months. Study 1 included 930 participants who received daridorexant 50 mg, 25 mg, or placebo (n = 310 for all). Study 2 participants received daridorexant 25 mg, 10 mg, or placebo (n = 309, 307, and 308, respectively).

The primary efficacy end point was change from baseline in latency to persistent sleep (LPS) and wake after sleep onset (WASO), measured by polysomnography at months 1 and 3. Secondary end points included patient-reported subjective total sleep time (sTST), recorded using a validated sleep diary questionnaire.

At months 1 and 3, study 1 participants who received 25 mg or 50 mg demonstrated statistically significant improvements in LPS, WASO, and sTST; study 2 results showed that 25 mg led to a statistically significant improvement vs placebo in WASO and sTST. No statistically significant improvement was noted in the 10 mg group.

**Safety**

The safety profile of daridorexant was established through 3 placebo-controlled studies: study 1, study 2, and a phase 3, 9-month extension study of eligible patients from the first 2 studies (NCT03679884). In the extension study, 804 participants were randomly assigned to receive daridorexant 50 mg, 25 mg, or 10 mg; placebo; or daridorexant 25 mg/ex-placebo.

The most common adverse events in the 25-mg, 50-mg, and placebo groups, respectively, were headache (6%, 7%, 5%), somnolence/fatigue (6%, 5%, 4%), dizziness (2%, 3%, 2%), and nausea (0%, 3%, 2%). Rare occurrences of sleep paralysis were reported in the 25-mg and 50-mg groups, and hypnagogic/hypnopompic hallucinations were reported in the 25-mg group.

**Drug Administration**

Daridorexant is for the treatment of adult patients with insomnia and is supplied as an arc triangle-shaped, film-coated oral tablet. The recommended dosage range is 25 mg to 50 mg taken by mouth, no more than once per night and wake after sleep onset (WASO), measured by polysomnography at months 1 and 3. Secondary end points included patient-reported subjective total sleep time (sTST), recorded using a validated sleep diary questionnaire.

At months 1 and 3, study 1 participants who received 25 mg or 50 mg demonstrated statistically significant improvements in LPS, WASO, and sTST; study 2 results showed that 25 mg led to a statistically significant improvement vs placebo in WASO and sTST. No statistically significant improvement was noted in the 10 mg group.

The use of daridorexant is contraindicated in patients with severe hepatic impairment; a maximum daily dose of 25 mg is recommended in those with moderate impairment. Concomitant use with strong CYP3A4 inhibitors should be avoided. Concomitant use with moderate inhibitors of CYP3A4 may be considered, but the maximum daily dose should not exceed 25 mg.

Daridorexant is a schedule IV medication with potential for abuse due to its central nervous system depressant effects.
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