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Janssen to Present Data from Robust Oncology Portfolio and Pipeline at the 2019 ASCO Annual Meeting, Including Best of ASCO Selections

- *First presentation of ERLEADA® (apalutamide) Phase 3 TITAN pivotal data in metastatic castration-sensitive prostate cancer*
- *DARZALEX® (daratumumab) first results from Phase 3 CASSIOPEIA trial as combination therapy for newly diagnosed transplant eligible multiple myeloma and Phase 3 COLUMBA pivotal data for a new subcutaneous formulation in relapsed/refractory multiple myeloma*
- *IMBRUVICA® (ibrutinib) Phase 3 RESONATE™ six-year follow-up data in relapsed/refractory chronic lymphocytic leukemia*
- *Updated data on investigational bispecific compound JNJ-61186372 in non-small cell lung cancer*

RARITAN, N.J., May 15, 2019 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today the latest research from its robust oncology portfolio and pipeline to be presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago from May 31 to June 4. More than 30 company-sponsored abstracts have been accepted, supporting the data from clinical development programs investigating innovative treatments for prostate cancer, hematologic malignancies and solid tumors. Notably, data presentations for ERLEADA® (apalutamide), DARZALEX® (daratumumab) and IMBRUVICA® (ibrutinib) have been selected for the Best of ASCO 2019 Meetings, which highlight cutting-edge science and reflect leading research in oncology.

"As we continue to advance our portfolio and pipeline, we are pleased to present important new findings for ERLEADA in metastatic castration-sensitive prostate cancer, and for DARZALEX in the treatment of newly diagnosed multiple myeloma and as a subcutaneous formulation," said Peter Lebowitz, M.D., Ph.D., Global Therapeutic Area Head, Oncology, Janssen Research & Development, LLC. "The ASCO Annual Meeting represents an important venue to present the very latest from our research and development programs, and showcase our commitment to improve the lives of patients who have been diagnosed with cancer through breakthrough science and innovative medicines."

Highlights of the data from Janssen's diverse oncology portfolio and pipeline include:

ERLEADA Results in the Treatment of Metastatic Castration-Sensitive Prostate Cancer
Results from the Phase 3 TITAN trial evaluating ERLEADA in combination with androgen deprivation therapy (ADT) in the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC) will be featured in an oral presentation (Abstract #5006). On April 29, Janssen announced the submission of a supplemental New Drug Application (sNDA) to the U.S. Food & Drug Administration (FDA) seeking approval of ERLEADA for the treatment of patients with mCSPC, based upon findings from TITAN, which met its dual primary endpoints, overall survival (OS) and radiographic progression-free survival (rPFS). The sNDA is being reviewed by the FDA through the Real-Time Oncology Review (RTOR) program.

DARZALEX Findings in the Treatment of Newly Diagnosed and Relapsed/Refractory Multiple Myeloma, Including Pivotal Subcutaneous Formulation Data
Data from two Phase 3 studies of DARZALEX will be presented during an oral session. Results from the Phase 3 CASSIOPEIA study evaluating DARZALEX in combination with bortezomib, thalidomide and dexamethasone for newly diagnosed patients with multiple myeloma who are transplant eligible will be presented (Abstract #8003). These data supported recent regulatory filings in the U.S. and European Union seeking to expand the current indication for DARZALEX in the frontline setting. Findings from the Phase 3 COLUMBA study will be presented (Abstract #8005) evaluating the subcutaneous formulation in the treatment of patients with relapsed/refractory multiple myeloma.

IMBRUVICA Long-Term Data in Chronic Lymphocytic Leukemia
Follow-up results from the Phase 3 RESONATE™ (PCYC-1112) study evaluating IMBRUVICA monotherapy in adult patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) will be presented (Abstract #7510). The final analysis with six years of follow-up continues to support long-term disease control and tolerability with

IMBRUVICA in the treatment of CLL/SLL. IMBRUVICA, a Bruton's tyrosine kinase (BTK) inhibitor, is jointly developed and commercialized by Janssen Biotech, Inc. and Pharmacyclics LLC, an AbbVie company.

Data for the Investigational Bispecific JNJ-61186372 in the Treatment of Patients with Non-Small Cell Lung Cancer

An oral presentation (Abstract #9009) will feature updated Phase 1 safety and efficacy results evaluating JNJ-61186372, a fully-humanized bispecific antibody targeting both the EGFR and MET tyrosine receptor kinases, in patients with advanced non-small cell lung cancer (NSCLC). JNJ-61186372 is currently being developed for the treatment of patients with EGFR-mutated NSCLC.

Select company-sponsored abstracts follow below. In addition, abstracts for ZYTIGA® (abiraterone acetate), VELCADE® (bortezomib) and YONDELIS® (trabectedin) will also be presented and can be found through the ASCO abstract database here.

Abstract No.	**Title**	**Date/Time**
ERLEADA (apalutamide)		
	Oral Presentation	
Abstract #5006	First results from TITAN: A phase 3 double-blind, randomized study of apalutamide versus placebo in patients with mCSPC receiving ADT	Friday, May 31 4:45 – 4:57 p.m. CT
	Poster Presentations	
Abstract #5023	Efficacy of apalutamide plus ongoing ADT in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) and baseline comorbidities	Saturday, June 1 1:15 – 4:15 p.m. CT
Abstract #5024	Age-related efficacy and safety of apalutamide plus ongoing (ADT) in subgroups of patients with nmCRPC: Post hoc analysis of SPARTAN	Saturday, June 1 1:15 – 4:15 p.m. CT
Abstract #5025	Predictors of falls and fractures in patients with nmCRPC treated with apalutamide plus ongoing ADT	Saturday, June 1 1:15 – 4:15 p.m. CT
Abstract # TPS5100	PROTEUS: A randomized, double-blind, placebo-controlled, phase 3 trial of apalutamide plus ADT versus placebo plus ADT prior to radical prostatectomy in patients with localized high-risk or locally advanced prostate cancer	Saturday, June 1 1:15 – 4:15 p.m. CT
DARZALEX (daratumumab)		
	Oral Presentations	
Abstract #8003	Phase 3 Randomized Study of Daratumumab + Bortezomib/Thalidomide/ Dexamethasone (D-VTd) Vs VTd in Transplant-eligible Newly Diagnosed Multiple Myeloma: CASSIOPEIA Part 1 Results	Sunday, June 2 10:45 – 10:57 a.m. CT

Abstract #8005	Efficacy and Safety of the Randomized, Open-Label, Non-inferiority, Phase 3 Study of Subcutaneous Versus Intravenous Daratumumab Administration in Patients with Relapsed or Refractory Multiple Myeloma: COLUMBA	Sunday, June 2 11:09 – 11:21 a.m. CT
Poster Discussions		
Abstract #8017	Efficacy of Daratumumab + VTd in Transplant-eligible Newly Diagnosed Multiple Myeloma Based on Minimal Residual Disease Status: Analysis of the CASSIOPEIA Trial	Monday, June 3 Poster Display: 8:00 – 11:00 a.m. CT Poster Discussion: 1:15 – 2:15 p.m. CT
Abstract #8016	Faster and sustained improvement in health-related quality of life for newly diagnosed multiple myeloma patients ineligible for transplant treated with daratumumab, lenalidomide, and dexamethasone (D-Rd) vs Rd alone: MAIA	Monday, June 3 Poster Display: 8:00 – 11:00 a.m. CT Poster Discussion: 1:15 – 2:15 p.m. CT
Poster Presentations		
Abstract #8042	Stem Cell Yield and Transplantation Results from Transplant-eligible Newly Diagnosed Multiple Myeloma Patients Receiving Daratumumab + VTd in the Phase 3 CASSIOPEIA Study	Monday, June 3 8:00 – 11:00 a.m. CT
Abstract #8035	Impact of Age on Efficacy and Safety of Daratumumab in Combination with Lenalidomide and Dexamethasone (D-Rd) in Patients with Transplant-ineligible Newly Diagnosed Multiple Myeloma: MAIA	Monday, June 3 8:00 – 11:00 a.m. CT
Abstract #8038	Efficacy and Safety of Daratumumab, Lenalidomide, and Dexamethasone (D-Rd) in Relapsed or Refractory Multiple Myeloma: Updated Subgroup Analysis of POLLUX Based on Cytogenetic Risk	Monday, June 3 8:00 – 11:00 a.m. CT
Abstract #8040	Efficacy and Safety of Daratumumab, Bortezomib, and Dexamethasone (D-Vd) in Relapsed or Refractory Multiple Myeloma Based on Cytogenetic Risk: Updated Subgroup Analysis of CASTOR	Monday, June 3 8:00 – 11:00 a.m. CT
Abstract # TPS8055	Bortezomib, lenalidomide, and dexamethasone (VRd) ± daratumumab in patients with transplant-eligible newly diagnosed multiple myeloma: a multicenter, randomized, Phase 3 study (PERSEUS)	Monday, June 3 8:00 – 11:00 a.m. CT
Abstract # TPS8056	Bortezomib, lenalidomide, and dexamethasone (VRd) ± daratumumab in patients with newly diagnosed multiple myeloma for whom transplant is not planned as initial therapy: a multicenter, randomized, phase 3 study (CEPHEUS).	Monday, June 3 8:00 – 11:00 a.m. CT
IMBRUVICA* (ibrutinib)		
Poster Discussions		
Abstract #7510	Final Analysis From RESONATE: 6-Year Follow-up in Patients with Previously Treated CLL/SLL on Ibrutinib	Monday, June 3 Poster Display: 8:00 – 11:00 a.m. CT Poster Discussion: 11:30 a.m. – 1:00 p.m. CT
Abstract #8018	Patient-Reported Outcomes with Ibrutinib-Rituximab in Waldenström Macroglobulinemia: Results From iNNOVATE™	Monday, June 3 Poster Display: 8:00 – 11:00 a.m. CT

		Poster Discussion: 1:15 – 2:45 p.m. CT
BALVERSA™ (erdafitinib)		
Poster Presentations		
Abstract #4117	Updated Results of a Ph2a Study to Evaluate the Clinical Efficacy and Safety of Erdafitinib in Asian Advanced Cholangiocarcinoma Patients with FGFR alterations	Monday, June 3 8:00 – 11:00 a.m. CT
Abstract #4542	FGFR-altered, advanced urothelial carcinoma (UC) and response to chemotherapy prior to receiving erdafitinib	Monday, June 3 1:15 – 4:15 p.m. CT
Abstract #4543	Erdafitinib in high-risk patients with advanced UC	Monday, June 3 1:15 – 4:15 p.m. CT
Niraparib		
Poster Presentations		
Abstract #TPS5087	A Phase 1b-2 Study of Niraparib Combination Therapies for the Treatment of Metastatic Castration-Resistant Prostate Cancer (mCRPC) (NCT03431350) QUEST	Saturday, June 1 1:15 – 4:15 p.m. CT
Abstract #5066	Plasma DNA repair deficient status associates with clinical outcome of mCRPC patients (pts) treated with abiraterone acetate plus prednisone/dexamethasone (+P/D)	Saturday, June 1 1:15 – 4:15 p.m. CT
JNJ-64457107		
Poster Presentation		
Abstract #2527	A phase I study to assess safety, pharmacokinetics, and pharmacodynamics of JNJ-64457107, a CD40 agonistic monoclonal antibody, in patients with advanced solid tumors	Saturday, June 1 8:00 – 11:00 a.m. CT
JNJ-61186372		
Oral Presentation		
Abstract #9009	JNJ-61186372, an EGFR-cMet bispecific antibody, in EGFR-driven advanced NSCLC	Friday, May 31 1:12 – 1:24 p.m. CT
XARELTO® (rivaroxaban)		
Poster Discussion		
Abstract #4016	Rivaroxaban thromboprophylaxis in ambulatory patients with pancreatic cancer: Results from a prespecified subgroup analysis of the CASSINI study	Monday, June 3 8:00 – 11:00 a.m. CT

*****Abstracts were submitted by IMBRUVICA co-developer partner, Pharmacyclics, an AbbVie company.

About ERLEADA® (apalutamide)

ERLEADA® (apalutamide) is an androgen receptor (AR) inhibitor indicated for the treatment of patients with nmCRPC. It became the first treatment to receive FDA approval for this disease state on February 14, 2018.[1] The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer include apalutamide as a treatment option for patients with non-metastatic (M0) CRPC with a category 1 recommendation for those with a PSA doubling time ≤10 months*.[2] Additionally, the American Urological Association (AUA) Guidelines for Castration-

Resistant Prostate Cancer (CRPC) were updated to include apalutamide (ERLEADA) with continued ADT as a treatment option that clinicians should offer to patients with asymptomatic nmCRPC. It is included as one of the options clinicians should offer to patients with nmCRPC who are at high-risk for developing metastatic disease (Standard; Evidence Level Grade A)**.[3]

**Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.2.2019. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed April 23, 2019. To view the most recent and complete version of the NCCN Guidelines®, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application, and disclaims any responsibility for their application or use in any way.*

***Standard: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade A or B evidence.*

***Evidence Level: A designation indicating the certainty of the results as high, moderate, or low (A, B, or C, respectively) based on AUA nomenclature and methodology.*

About DARZALEX® (daratumumab)

DARZALEX® (daratumumab), the first CD38-directed antibody approved anywhere in the world, is the only CD38-directed antibody approved to treat multiple myeloma.[4] CD38 is a surface protein that is present in high numbers on multiple myeloma cells, regardless of the stage of disease.[5] DARZALEX binds to CD38 and inhibits tumor cell growth causing myeloma cell death.**Error! Bookmark not defined.** DARZALEX may also have an effect on normal cells.**Error! Bookmark not defined.** DARZALEX is being evaluated in a comprehensive clinical development program across a range of treatment settings in multiple myeloma, such as in frontline and relapsed settings.[6,7,8,9,10,11,12,13] Additional studies are ongoing or planned to assess its potential in other malignant and pre-malignant hematologic diseases in which CD38 is expressed, such as smoldering myeloma.[14,15]

In the U.S., DARZALEX received initial FDA approval in November 2015 as a monotherapy for patients with multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent, or who are double refractory to a PI and an immunomodulatory agent.[16] DARZALEX received additional approvals in November 2016 in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.[17] In June 2017, DARZALEX received approval in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least

two prior therapies, including lenalidomide and a PI.[18] In May 2018, DARZALEX received approval in combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for ASCT, making it the first monoclonal antibody approved for newly diagnosed patients with this disease.[19]

In August 2012, Janssen Biotech, Inc. entered into a global license and development agreement with Genmab A/S, which granted Janssen an exclusive license to develop, manufacture and commercialize DARZALEX.[20] For the full U.S. Prescribing Information, please visit www.DARZALEX.com.

About IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) is a once-daily oral medicine that works differently than chemotherapy as it blocks the Bruton's tyrosine kinase (BTK) protein. The BTK protein sends important signals that tell B cells to mature and produce antibodies. BTK signaling is needed by specific cancer cells to multiply and spread.[21,22] By blocking BTK, IMBRUVICA may help move abnormal B cells out of their nourishing environments in the lymph nodes, bone marrow, and other organs.[23]

IMBRUVICA is approved in more than 95 countries, and, to date, has been used to treat more than 140,000 patients worldwide across approved indications. It was first approved by the U.S. Food and Drug Administration (FDA) in November 2013, and today is indicated in six disease areas, including five hematologic cancers – chronic lymphocytic leukemia (CLL) with or without 17p deletion (del17p), small lymphocytic lymphoma (SLL) with or without del17p, Waldenström's macroglobulinemia (WM), previously-treated patients with mantle cell lymphoma (MCL)*, previously-treated patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy*, and previously-treated patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.[24]

IMBRUVICA is the first and only FDA-approved medicine in WM, MZL* and cGVHD. IMBRUVICA has been granted four Breakthrough Therapy Designations by the FDA, and it was one of the first medicines to receive U.S. approval through the Breakthrough Therapy Designation.

** Accelerated approval was granted for MCL and MZL based on overall response rate. Continued approval for MCL and MZL may be contingent upon verification and description of clinical benefit in confirmatory trials.*

IMBRUVICA is a comprehensively studied molecule in the oncology industry. The robust clinical oncology development program includes more than 150 active clinical trials studying IMBRUVICA

alone and in combination with other medicines in several blood cancers and other serious diseases. For more information, visit www.IMBRUVICA.com.

About BALVERSA™ (erdafitinib)

BALVERSA™ (erdafitinib) is a once-daily, oral fibroblast growth factor receptor (FGFR) kinase inhibitor indicated for the treatment of adults with locally advanced or metastatic urothelial carcinoma (mUC) that has susceptible FGFR3 or FGFR2 genetic alterations and who have progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.[25] This indication is approved under accelerated approval based on tumor response rate. Select patients for therapy based on an FDA-approved companion diagnostic for BALVERSA. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.[25]

The pivotal multicenter, open-label Phase 2 BLC2001 (NCT02365597) clinical trial evaluated the efficacy and safety of BALVERSA for the treatment of adults with locally advanced or mUC that had progressed on or after at least one line of prior chemotherapy and whose tumors have certain FGFR alterations.[25] In 2008, Janssen entered into an exclusive worldwide license and collaboration agreement with Astex Pharmaceuticals to develop and commercialize BALVERSA. BALVERSA is commercially available through the single-source specialty pharmacy provider US Bioservices.

For more information about BALVERSA, visit www.BALVERSA.com.

About niraparib

Niraparib is an orally-administered selective poly ADP ribose polymerase (PARP) inhibitor that is currently being studied for the treatment of patients with prostate cancer by Janssen. In April 2016, Janssen entered a worldwide (except Japan) collaboration and license agreement with TESARO, Inc., for exclusive rights to niraparib in prostate cancer. In the U.S., niraparib is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.[26] Niraparib is currently marketed by TESARO, an oncology-focused business within GSK, devoted to providing transformative therapies to people facing cancer. Please refer to the full Prescribing Information available at http://www.tesarobio.com/en/products/zejula-niraparib.

WHAT IS XARELTO® (rivaroxaban)?[27]

XARELTO® (rivaroxaban) is a prescription medicine used to:

- reduce the risk of stroke and blood clots in people who have a medical condition called atrial fibrillation that is not caused by a heart valve problem. With atrial fibrillation, part of the heart does not beat the way it should. This can lead to the formation of blood clots, which can travel to the brain, causing a stroke, or to other parts of the body
- treat blood clots in the veins of your legs (deep vein thrombosis or DVT) or lungs (pulmonary embolism or PE)
- reduce the risk of blood clots happening again in people who continue to be at risk for DVT or PE after receiving treatment for blood clots for at least 6 months
- help prevent a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery

XARELTO® is also used with low dose aspirin to:

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

It is not known if XARELTO® is safe and effective in children.

ERLEADA™ IMPORTANT SAFETY INFORMATION[1]
CONTRAINDICATIONS

Pregnancy — ERLEADA™ (apalutamide) can cause fetal harm and potential loss of pregnancy.

WARNINGS AND PRECAUTIONS

Falls and Fractures — In a randomized study (SPARTAN), falls and fractures occurred in 16% and 12% of patients treated with ERLEADA™ compared to 9% and 7% treated with placebo, respectively. Falls were not associated with loss of consciousness or seizure. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone targeted agents.

Seizure — In a randomized study (SPARTAN), 2 patients (0.2%) treated with ERLEADA™ experienced a seizure. Permanently discontinue ERLEADA™ in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA™. Advise patients of the risk of developing a seizure while receiving ERLEADA™ and of

engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

ADVERSE REACTIONS

Adverse Reactions — The most common adverse reactions (≥10%) were fatigue, hypertension, rash, diarrhea, nausea, weight decreased, arthralgia, fall, hot flush, decreased appetite, fracture, and peripheral edema.

Laboratory Abnormalities — All Grades (Grade 3-4)

- Hematology — anemia ERLEADA™ 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA™ 47% (0.3%), placebo 29% (0%); lymphopenia ERLEADA™ 41% (2%), placebo 21% (2%)

- Chemistry — hypercholesterolemia ERLEADA™ 76% (0.1%), placebo 46% (0%); hyperglycemia ERLEADA™ 70% (2%), placebo 59% (1%); hypertriglyceridemia ERLEADA™ 67% (2%), placebo 49% (0.8%); hyperkalemia ERLEADA™ 32% (2%), placebo 22% (0.5%)

Rash — Rash was most commonly described as macular or maculo-papular. Adverse reactions were 24% with ERLEADA™ versus 6% with placebo. Grade 3 rashes (defined as covering > 30% body surface area [BSA]) were reported with ERLEADA™ treatment (5%) versus placebo (0.3%).

The onset of rash occurred at a median of 82 days. Rash resolved in 81% of patients within a median of 60 days (range: 2 to 709 days) from onset of rash. Four percent of patients treated with ERLEADA™ received systemic corticosteroids. Rash recurred in approximately half of patients who were re-challenged with ERLEADA™.

Hypothyroidism was reported for 8% of patients treated with ERLEADA™ and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA™ and 7% of patients treated with placebo. The median onset was day 113. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA™ — Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA™ dose based on tolerability *[see Dosage and Administration (2.2)].*

Effect of ERLEADA™ on Other Drugs — ERLEADA™ is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA™ with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA™ with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA™ and evaluate for loss of activity.

P-gp, BCRP or OATP1B1 substrates — Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. Concomitant use of ERLEADA™ with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with ERLEADA™ and evaluate for loss of activity if medication is continued.

Please see the full Prescribing Information for ERLEADA™.

DARZALEX® (daratumumab) IMPORTANT SAFETY INFORMATION[4]

CONTRAINDICATIONS

DARZALEX® is contraindicated in patients with a history of severe hypersensitivity (e.g., anaphylactic reactions) to daratumumab or any of the components of the formulation.

WARNINGS AND PRECAUTIONS

Infusion Reactions – DARZALEX® can cause severe and/or serious infusion reactions, including anaphylactic reactions. In clinical trials, approximately half of all patients experienced an infusion reaction. Most infusion reactions occurred during the first infusion and were grade 1-2. Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing an infusion. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as

chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension.

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt infusion for reactions of any severity and institute medical management as needed. Permanently discontinue therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients following DARZALEX® infusions. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Interference with Serological Testing – Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion.
Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX®. Type and screen patients prior to starting DARZALEX®.

Neutropenia – DARZALEX® may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. DARZALEX® dose delay may be required to allow recovery of neutrophils. No dose reduction of DARZALEX® is recommended. Consider supportive care with growth factors.

Thrombocytopenia – DARZALEX® may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. DARZALEX® dose delay may be required to allow recovery of platelets. No dose reduction of DARZALEX® is recommended. Consider supportive care with transfusions.

Interference with Determination of Complete Response – Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Adverse Reactions – The most frequently reported adverse reactions (incidence ≥20%) in clinical trials were: infusion reactions, neutropenia, thrombocytopenia, fatigue, nausea, diarrhea, constipation, vomiting, muscle spasms, arthralgia, back pain, pyrexia, chills, dizziness, insomnia, cough, dyspnea, peripheral edema, peripheral sensory neuropathy and upper respiratory tract infection.

In patients who received DARZALEX® in combination with bortezomib, melphalan, and prednisone (DVMP), the most frequently reported adverse reactions (incidence ≥20%) were: upper respiratory tract infection (48%), infusion reactions (28%), and peripheral edema (21%). Serious adverse reactions (≥2% compared to the VMP arm) were pneumonia (11%), upper respiratory tract infection (5%), and pulmonary edema (2%). Treatment-emergent Grade 3-4 hematology laboratory abnormalities ≥20% were lymphopenia (58%), neutropenia (44%), and thrombocytopenia (38%).

In patients who received DARZALEX® in combination with lenalidomide and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: upper respiratory tract infection (65%), infusion reactions (48%), diarrhea (43%), fatigue (35%), cough (30%), muscle spasms (26%), nausea (24%), dyspnea (21%) and pyrexia (20%). The overall incidence of serious adverse reactions was 49%. Serious adverse reactions (≥2% compared to Rd) were pneumonia (12%), upper respiratory tract infection (7%), influenza (3%), and pyrexia (3%). Treatment-emergent Grade 3-4 hematology laboratory abnormalities ≥20% were neutropenia (53%) and lymphopenia (52%).

In patients who received DARZALEX® in combination with bortezomib and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: peripheral sensory neuropathy (47%), infusion reactions (45%), upper respiratory tract infection (44%), diarrhea (32%), cough (27%), peripheral edema (22%), and dyspnea (21%). The overall incidence of serious adverse reactions was 42%. Serious adverse reactions (≥2% compared to Vd) were upper respiratory tract infection (5%), diarrhea (2%) and atrial fibrillation (2%). Treatment-emergent Grade 3-4 hematology laboratory abnormalities ≥20% were lymphopenia (48%) and thrombocytopenia (47%).

In patients who received DARZALEX® in combination with pomalidomide and dexamethasone, the most frequent adverse reactions (>20%) were fatigue (50%), infusion reactions (50%), upper respiratory tract infection (50%), cough (43%), diarrhea (38%), constipation (33%), dyspnea (33%), nausea (30%), muscle spasms (26%), back pain (25%), pyrexia (25%), insomnia (23%), arthralgia (22%), dizziness (21%), and vomiting (21%). The overall incidence of serious adverse reactions was 49%. Serious adverse reactions reported in ≥5% patients included pneumonia (7%). Treatment-emergent hematology Grade 3-4 laboratory abnormalities ≥20% were anemia (30%), neutropenia (82%), and lymphopenia (71%).

In patients who received DARZALEX® as monotherapy, the most frequently reported adverse reactions (incidence ≥20%) were: infusion reactions (48%), fatigue (39%), nausea (27%), back pain (23%), pyrexia (21%), cough (21%), and upper respiratory tract infection (20%). The overall incidence of serious adverse reactions was 33%. The most frequent serious adverse reactions were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%). Treatment-emergent Grade 3-4 hematology laboratory abnormalities ≥20% were lymphopenia (40%) and neutropenia (20%).

DRUG INTERACTIONS

Effect of Other Drugs on Daratumumab: The coadministration of lenalidomide, pomalidomide or bortezomib with DARZALEX® did not affect the pharmacokinetics of daratumumab.

Effect of Daratumumab on Other Drugs: The coadministration of DARZALEX® with bortezomib or pomalidomide did not affect the pharmacokinetics of bortezomib or pomalidomide.

Please see the full Prescribing Information for DARZALEX®.

IMBRUVICA® (ibrutinib) IMPORTANT SAFETY INFORMATION[24]

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 3% of patients, with fatalities occurring in 0.3% of 1,124 patients exposed to IMBRUVICA® in clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 44% of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood.

IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding.

Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 24% of 1,124 patients exposed to IMBRUVICA® in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA®.

Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA® therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,124 patients exposed to IMBRUVICA® in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines**.**

Hypertension: Hypertension of any grade occurred in 12% of 1,124 patients treated with IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 5% of patients with a median time to onset of 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA® and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate.

Second Primary Malignancies: Other malignancies (10%) including non-skin carcinomas (4%) have occurred in 1,124 patients treated with IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA® therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions.

Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Advise men to avoid fathering a child during the same time period.

ADVERSE REACTIONS

B-cell malignancies: The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (58%)*, diarrhea (41%), anemia (38%)*, neutropenia (35%)*, musculoskeletal pain (32%), rash (32%), bruising (31%), nausea (26%), fatigue (26%), hemorrhage (24%), and pyrexia (20%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (18%)*, thrombocytopenia (16%)*, and pneumonia (14%).

Approximately 7% (CLL/SLL), 14% (MCL), 14% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions. Approximately 4-10% (CLL/SLL), 9% (MCL), and 7% (WM [5%] and MZL [13%]) of patients discontinued due to adverse reactions.

cGVHD: The most common adverse reactions (≥20%) in patients with cGVHD were fatigue (57%), bruising (40%), diarrhea (36%), thrombocytopenia (33%)*, muscle spasms (29%), stomatitis (29%), nausea (26%), hemorrhage (26%), anemia (24%)*, and pneumonia (21%).

The most common Grade 3 or higher adverse reactions (≥5%) reported in patients with cGVHD were pneumonia (14%), fatigue (12%), diarrhea (10%), neutropenia (10%)*, sepsis (10%), hypokalemia (7%), headache (5%), musculoskeletal pain (5%), and pyrexia (5%).

Twenty-four percent of patients receiving IMBRUVICA® in the cGVHD trial discontinued treatment due to adverse reactions. Adverse reactions leading to dose reduction occurred in 26% of patients.

*Treatment-emergent decreases (all grades) were based on laboratory measurements.

DRUG INTERACTIONS

CYP3A Inhibitors: Modify IMBRUVICA® dose as described in USPI sections 2.4 and 7.1.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe baseline hepatic impairment. In patients with mild or moderate impairment, reduce IMBRUVICA® dose.

Please click here for full Prescribing Information.

BALVERSA™ (erdafitinib) IMPORTANT SAFETY INFORMATION[25]

Ocular Disorders - BALVERSA™ can cause ocular disorders, including central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED) resulting in visual field defect.

CSR/RPED was reported in 25% of patients treated with BALVERSA™, with a median time to first onset of 50 days. Grade 3 CSR/RPED, involving central field of vision, was reported in 3% of patients. CSR/RPED resolved in 13% of patients and was ongoing in 13% of patients at the study cutoff. CSR/RPED led to dose interruptions and reductions in 9% and 14% of patients, respectively and 3% of patients discontinued BALVERSA™. Dry eye symptoms occurred in 28% of patients during treatment with BALVERSA™ and were Grade 3 in 6% of patients. All patients should receive dry eye prophylaxis with ocular demulcents as needed.

Perform monthly ophthalmological examinations during the first 4 months of treatment and every 3 months afterwards, and urgently at any time for visual symptoms. Ophthalmological examination should include assessment of visual acuity, slit lamp examination, fundoscopy, and optical coherence tomography. Withhold BALVERSA™ when CSR occurs and permanently discontinue if it does not resolve within 4 weeks or if Grade 4 in severity. For ocular adverse reactions, follow the dose modification guidelines *[see Dosage and Administration (2.3)]*.

Hyperphosphatemia - Increases in phosphate levels are a pharmacodynamic effect of BALVERSA™ *[see Pharmacodynamics (12.2)].* Hyperphosphatemia was reported as adverse reaction in 76% of patients treated with BALVERSA™. The median onset time for any grade event of hyperphosphatemia was 20 days (range: 8-116) after initiating BALVERSA™. Thirty-two percent of patients received phosphate binders during treatment with BALVERSA™. Monitor for hyperphosphatemia and follow the dose modification guidelines when required *[see Dosage and Administration (2.2, 2.3)]*.

Embryo-fetal Toxicity - Based on the mechanism of action and findings in animal reproduction studies, BALVERSA™ can cause fetal harm when administered to a pregnant woman. In a rat embryo-fetal toxicity study, erdafitinib was embryotoxic and teratogenic at exposures less than the human exposures at all doses studied. Advise pregnant women of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception prior to and during treatment, and for one month after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with BALVERSA™ and for one month after the last dose *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

Most common adverse reactions including laboratory abnormalities ≥ 20% were: Phosphate increased (76%), stomatitis (56%), fatigue (54%), creatinine increased (52%), diarrhea (47%), dry mouth (45%), onycholysis (41%), alanine aminotransferase increased (41%), alkaline phosphatase increased (41%), sodium decreased (40%), decreased appetite (38%), albumin decreased (37%), dysgeusia (37%), hemoglobin decreased (35%), dry skin (34%), aspartate aminotransferase increased (30%), magnesium decreased (30%), dry eye (28%), alopecia (26%), palmar-plantar erythrodysesthesia syndrome (26%), constipation (28%), phosphate decreased (24%), abdominal pain (23%), calcium increased (22%), nausea (21%), and musculoskeletal pain (20%). The most common Grade 3 or greater adverse reactions (>1%) were stomatitis (9%), nail dystrophy*, palmar-plantar erythrodysesthesia syndrome (6%), paronychia (3%), nail disorder*, keratitis[†], onycholysis* (10%), and hyperphosphatemia.
*Included within onycholysis. ^Included within dry eye.

An adverse reaction with a fatal outcome in 1% of patients was acute myocardial infarction.

Serious adverse reactions occurred in 41% of patients, including eye disorders (10%).

Permanent discontinuation due to an adverse reaction occurred in 13% of patients. The most frequent reasons for permanent discontinuation included eye disorders (6%).

Dosage interruptions occurred in 68% of patients. The most frequent adverse reactions requiring dosage interruption included hyperphosphatemia (24%), stomatitis (17%), eye disorders (17%), and palmar-plantar erythrodysesthesia syndrome (8%).

Dose reductions occurred in 53% of patients. The most frequent adverse reactions for dose reductions included eye disorders (23%), stomatitis (15%), hyperphosphatemia (7%), palmar-plantar erythrodysesthesia syndrome (7%), paronychia (7%), and nail dystrophy (6%).

Drug Interactions

- Strong CYP2C9 or CYP3A4 Inhibitors: Consider alternative agents or monitor closely for adverse reactions. (7.1)
- Strong CYP2C9 or CYP3A4 inducers: Avoid concomitant use with BALVERSA™. (7.1)
- Moderate CYP2C9 or CYP3A4 inducers: Increase BALVERSA™ dose up to 9 mg. (7.1)
- Serum phosphate level-altering agents: Avoid concomitant use with agents that can alter serum phosphate levels before the initial dose modification period. (2.3, 7.1)
- CYP3A4 substrates: Avoid concomitant use with sensitive CYP3A4 substrates with narrow therapeutic indices. (7.2)
- OCT2 substrates: Consider alternative agents or consider reducing the dose of OCT2 substrates based on tolerability. (7.2)
- P-gp substrates: Separate BALVERSA™ administration by at least 6 hours before or after administration of P-gp substrates with narrow therapeutic indices. (7.2)

Please click here for full prescribing information.

XARELTO® (rivaroxaban) IMPORTANT SAFETY INFORMATION[27]

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

A. Premature discontinuation of XARELTO® increases the risk of thrombotic events

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

B. Spinal/epidural hematoma

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

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

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

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

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to XARELTO® (e.g., anaphylactic reactions)

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including XARELTO®, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO® to warfarin in clinical trials in atrial

fibrillation patients. If XARELTO® is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

- **Risk of Bleeding:** XARELTO® increases the risk of bleeding and can cause serious or fatal bleeding. Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue in patients with active pathological hemorrhage.

  - An agent to reverse the anti-factor Xa activity of rivaroxaban is available. Because of high plasma protein binding, rivaroxaban is not dialyzable.
  - 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).

- **Spinal/Epidural Anesthesia or Puncture:** When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis. To reduce the potential risk of bleeding associated with concurrent use of XARELTO® and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of XARELTO®. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of XARELTO® is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. An indwelling epidural or intrathecal catheter should not be removed before at least 2 half-lives have elapsed (ie, 18 hours in young patients aged 20 to 45 years and 26 hours in elderly patients aged 60 to 76 years), after the last administration of XARELTO®. The next dose should not be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of XARELTO® for 24 hours. Monitor frequently to detect signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), or bowel and/or bladder dysfunction. Instruct patients to immediately report any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

- **Use in Patients with Renal Impairment:**

  - **Nonvalvular Atrial Fibrillation:** Periodically assess renal function as clinically indicated (ie, more frequently in situations in which renal function may decline) and adjust therapy accordingly. Consider dose adjustment or discontinuation in patients who develop acute

renal failure while on XARELTO®. Clinical efficacy and safety studies with XARELTO® did not enroll patients with CrCl ⩽30 mL/min or end-stage renal disease (ESRD) on dialysis.

- **Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE:** Avoid the use of XARELTO® in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamics effects in this patient population.
- **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:** Avoid the use of XARELTO® in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamics effects in this patient population. Observe closely and promptly evaluate signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on XARELTO® should discontinue treatment.
- **Reduction of Risk of Major Cardiovascular Events in Patients with Chronic CAD or PAD:** For patients with CrCl <15 mL/min, no data are available, and limited data are available for patients with a CrCl of 15-30 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, 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.

- **Use in Patients with Hepatic Impairment:** No clinical data are available for patients with severe hepatic impairment. Avoid use in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy, since drug exposure and bleeding risk may be increased.
- **Use with P-gp and Strong CYP3A Inhibitors or Inducers:** Avoid concomitant use of XARELTO® with known combined P-gp and strong CYP3A inhibitors or inducers.
- **Risk of Pregnancy-Related Hemorrhage:** In pregnant women, XARELTO® should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO® dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO® cannot be monitored with standard laboratory testing. Promptly evaluate signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).
- **Patients with Prosthetic Heart Valves:** Safety and efficacy of XARELTO® have not been studied in patients with prosthetic heart valves. Use of XARELTO® is not recommended in these patients.

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** The limited available data on XARELTO® in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Use XARELTO® with caution in pregnant patients because of the potential for pregnancy-related hemorrhage and/or emergent delivery. The anticoagulant effect of XARELTO® cannot be reliably monitored with standard laboratory testing. Consider the benefits and risks of XARELTO® for the mother and possible risks to the fetus when prescribing to a pregnant woman.
  - Fetal/Neonatal adverse reactions: Based on the pharmacologic activity of Factor Xa inhibitors and the potential to cross the placenta, bleeding may occur at any site in the fetus and/or neonate.
  - Labor or delivery: The risk of bleeding should be balanced with the risk of thrombotic events when considering use in this setting.
  - There are no adequate or well-controlled studies of XARELTO® in pregnant women, and dosing for pregnant women has not been established. Post-marketing experience is currently insufficient to determine a rivaroxaban-associated risk for major birth defects or

miscarriage.

- **Lactation:** Rivaroxaban has been detected in human milk. There are insufficient data to determine the effects of rivaroxaban on the breastfed child or on milk production. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for XARELTO® and any potential adverse effects on the breastfed infant from XARELTO® or from the underlying maternal condition.
- **Females and Males of Reproductive Potential:** Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.
- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

OVERDOSAGE

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

ADVERSE REACTIONS IN CLINICAL STUDIES

- Most common adverse reactions with XARELTO® were bleeding complications.

Please click here for full Prescribing Information, including Boxed WARNINGS.

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Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding ERLEADA, DARZALEX, IMBRUVICA and JNJ-372. The

reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Research & Development, LLC, any of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended December 30, 2018, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's most recently filed Quarterly Report on Form 10-Q, and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

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[1] ERLEADA U.S. Prescribing Information, February 2018.
[2] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.4.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Updated March 12, 2018.
[3] American Urological Association. Castration-Resistant Prostate Cancer Guidelines. http://www.auanet.org/guidelines/castration-resistant-prostate-cancer-(2013-amended-2018). Accessed May 2019.
[4] DARZALEX U.S. Prescribing Information, June 2018.
[5] Fedele G et al. CD38 Ligation in Peripheral Blood Mononuclear Cells of Myeloma Patients Induces Release of Protumorigenic IL-6 and Impaired Secretion of IFNγ Cytokines and Proliferation. Mediators Inflamm. 2013;564687.
[6] Janssen Research & Development, LLC. A Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 July 24]. Available at: https://clinicaltrials.gov/ct2/show/NCT02076009?term=mmy3003&rank=1 Identifier: NCT02136134.
[7] Janssen Research & Development, LLC. Addition of Daratumumab to Combination of Bortezomib and Dexamethasone in Participants With Relapsed or Refractory Multiple Myeloma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 July 24]. Available at: https://clinicaltrials.gov/ct2/show/NCT02136134?term=mmy3004&rank=1 Identifier: NCT02076009.
[8] Janssen Research & Development, LLC. A Study to Evaluate Daratumumab in Transplant Eligible Participants With Previously Untreated Multiple Myeloma (Cassiopeia). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 July 24]. Available at: https://clinicaltrials.gov/ct2/show/NCT02541383?term=mmy3006&rank=2 NLM Identifier: NCT02541383.
[9] Janssen Research & Development, LLC. A Study of Combination of Daratumumab and Velcade (Bortezomib) Melphalan-Prednisone (DVMP) Compared to Velcade Melphalan-Prednisone (VMP) in Participants With Previously Untreated Multiple Myeloma In: ClinicalTrials.gov [Internet]. Bethesda (MD):

National Library of Medicine (US). 2000-[cited 2018 July 24]. Available at: https://clinicaltrials.gov/ct2/show/NCT02195479?term=mmy3007&rank=1 Identifier: NCT02195479.
[10] Janssen Research & Development, LLC. Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Participants With Previously Untreated Multiple Myeloma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 July 24]. Available at: https://clinicaltrials.gov/ct2/show/NCT02252172?term=mmy3008&rank=1 Identifier: NCT02252172.
[11] Janssen Research & Development, LLC. A Study of VELCADE (Bortezomib) Melphalan-Prednisone (VMP) Compared to Daratumumab in Combination With VMP (D-VMP), in Participants With Previously Untreated Multiple Myeloma Who Are Ineligible for High-Dose Therapy (Asia Pacific Region). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 July 24]. Available at: https://clinicaltrials.gov/ct2/show/NCT03217812?term=MMY3011&rank=1 Identifier: NCT03217812.
[12] European Myeloma Network. Compare Progression Free Survival Btw Daratumumab/Pomalidomide/Dexamethasone vs Pomalidomide/Dexamethasone (EMN14). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 July 24] Available at: https://clinicaltrials.gov/ct2/show/NCT03180736?term=MMY3013&rank=2 Identifier: NCT03180736
[13] Amgen. Study of Carfilzomib, Daratumumab and Dexamethasone for Patients With Relapsed and/or Refractory Multiple Myeloma. (CANDOR). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 July 24] Available at: https://clinicaltrials.gov/ct2/show/NCT03158688?term=NCT03158688&rank=1 Identifier: NCT03158688.
[14] Janssen Research & Development, LLC. A Study to Evaluate 3 Dose Schedules of Daratumumab in Participants With Smoldering Multiple Myeloma In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 March 19]. Available at: https://clinicaltrials.gov/ct2/show/NCT02316106?term=smm2001&rank=1 Identifier: NCT02316106.
[15] Janssen Research & Development, LLC. An Efficacy and Safety Proof of Concept Study of Daratumumab in Relapsed/Refractory Mantle Cell Lymphoma, Diffuse Large B-Cell Lymphoma, and Follicular Lymphoma In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 March 19]. Available at: https://clinicaltrials.gov/ct2/show/NCT02413489?term=lym2001&rank=1 Identifier: NCT02413489
[16] Janssen Biotech, Inc. "DARZALEX® (daratumumab) Approved by U.S. FDA: First Human Anti-CD38 Monoclonal Antibody Available for the Treatment of Multiple Myeloma." Issued November 16, 2015.
[17] Janssen Biotech, Inc. "DARZALEX® (daratumumab) Approved by U.S. FDA in Combination with Two Standard of Care Regimens for the Treatment of Patients with Multiple Myeloma Who Have Received At Least One Prior Therapy." Issued November 21, 2016.
[18] Janssen Biotech, Inc. "DARZALEX® (daratumumab) Approved by the U.S. FDA in Combination with Pomalidomide and Dexamethasone for Patients with Multiple Myeloma Who Have Received At Least Two Prior Therapies." Issued June 16, 2017.
[19] Janssen Pharmaceutical Companies of Johnson & Johnson. "Janssen Announces DARZALEX® (daratumumab) U.S. FDA Approval for Newly Diagnosed Patients with Multiple Myeloma who are Transplant Ineligible." Issued May 7, 2018.
[20] Janssen Biotech, Inc. "Janssen Biotech Announces Global License and Development Agreement for Investigational Anti-Cancer Agent Daratumumab." Issued August 30, 2012.
[21] Genetics Home Reference. Isolated growth hormone deficiency. http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency. Accessed May 2019.
[22] Turetsky, et al. Single cell imaging of Bruton's Tyrosine Kinase using an irreversible inhibitor. Scientific Reports. volume 4, Article number: 4782 (2014).
[23] de Rooij MF, Kuil A, Geest CR, et al. The clinically active BTK inhibitor PCI-32765 targets B-cell receptor- and chemokine-controlled adhesion and migration in chronic lymphocytic leukemia. Blood. 2012;119(11):2590-2594.
[24] IMBRUVICA U.S. Prescribing Information, January 2019.
[25] BALVERSA US Prescribing Information, April 2019.
[26] Niraparib U.S. Prescribing Information.
[27] XARELTO U.S. Prescribing Information.