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

- DARZALEX significantly improved progression-free survival (PFS) in combination with two standard of care regimens versus standard of care regimens alone
- Approval based on two Phase 3 studies showing consistent and pronounced clinical benefit of DARZALEX in combination with two of the most widely used treatment classes for multiple myeloma

HORSHAM, PA, November 21, 2016 – Janssen Biotech, Inc. announced today the U.S. Food and Drug Administration (FDA) has approved DARZALEX® (daratumumab) 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.¹ Clinical studies have shown that DARZALEX, in combination with lenalidomide (an immunomodulatory agent) and dexamethasone, reduced the risk of disease progression or death by 63 percent, compared to lenalidomide and dexamethasone alone, in patients with multiple myeloma who received a median of one prior therapy (Hazard Ratio [HR]=0.37; 95 percent CI [0.27, 0.52], p<0.0001).¹ In combination with bortezomib (a proteasome inhibitor [PI]) and dexamethasone, DARZALEX reduced the risk of disease progression or death by 61 percent, compared to bortezomib and dexamethasone alone, in patients with multiple myeloma who received a median of two prior lines of therapy (HR=0.39; 95 percent CI [0.28, 0.53], p<0.0001).¹ Multiple myeloma is an incurable blood cancer that occurs when malignant plasma cells grow uncontrollably in the bone marrow.²,³
The approval comes three months after a supplemental Biologics License Application (sBLA) was submitted to the FDA in August 2016.\textsuperscript{4} DARZALEX received Breakthrough Therapy Designation from the FDA for this indication in July 2016.\textsuperscript{5}

“While tremendous progress in the treatment of multiple myeloma has been made in the past decade, patients and their physicians continue to need new treatment options,” said Meletios A. Dimopoulos, M.D., Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, Alexandra General Hospital, Athens, Greece, a DARZALEX clinical trial investigator. “With DARZALEX, we have a potential new backbone therapy, which has shown pronounced efficacy as either a single agent or in combination with standard of care regimens. The addition of DARZALEX also significantly improved progression-free survival in combination with two of the most widely used treatment classes, making it a versatile option for patients who have received at least one prior therapy.”

DARZALEX is the first CD38-directed cytolytic antibody approved anywhere in the world.\textsuperscript{6} It was first approved by the FDA in November 2015 as a monotherapy treatment for patients with multiple myeloma who have received at least three prior lines of therapy, including a PI and an immunomodulatory agent, or who are double refractory to a PI and immunomodulatory agent.\textsuperscript{1}

Today’s approval is supported by data from two Phase 3 studies:

- According to results from the open-label POLLUX (MMY3003) clinical study, the median progression-free survival (PFS) in the DARZALEX arm has not been reached, compared with a median PFS of 18.4 months for patients who received lenalidomide and dexamethasone alone, with a median follow-up of 13.5 months.\textsuperscript{1} In addition to meeting the primary endpoint of improved PFS, DARZALEX significantly increased the overall response rate (ORR) [91 percent vs. 75 percent, p<0.0001], compared to lenalidomide and dexamethasone alone, including doubling rates of complete response (CR) [25 percent vs. 12 percent, p<0.0001] and significantly increasing very good partial response (VGPR) [32 percent vs. 24 percent, p<0.0001].\textsuperscript{1} These results were published in \textit{The New England Journal of Medicine}, with an accompanying editorial, in October 2016.\textsuperscript{7}

- According to results from the open-label CASTOR (MMY3004) clinical study, the median PFS in the DARZALEX arm has not been reached, compared with a median PFS of 7.2 months for patients who received bortezomib and dexamethasone alone, with a median follow-up of 7.4 months.\textsuperscript{1} In addition to meeting the primary endpoint of improved PFS, DARZALEX also significantly increased ORR [79 percent vs. 60 percent, p<0.0001], compared to bortezomib and dexamethasone alone, including doubling rates of CR [14 percent vs. 7 percent, p<0.0001] and...
significantly increasing VGPR [38 percent vs. 19 percent, p<0.0001].¹ These results were published in *The New England Journal of Medicine* in August 2016.⁸

Updated results from these clinical studies will be presented as oral presentations at the 58th American Society of Hematology (ASH) Annual Meeting to be held in San Diego, CA from December 3-6, 2016 (Abstract #1150; Abstract #1151).

“The approval of daratumumab provides multiple myeloma patients with another versatile treatment option to help address their urgent medical needs,” said Paul Giusti, President and Chief Executive Officer of the Multiple Myeloma Research Foundation (MMRF). “At the MMRF, we are excited by the groundbreaking work being done to bring effective, new treatments to patients.”

“We are proud of the rapid development and approval of DARZALEX for use earlier in the treatment pathway, but our work does not stop here,” said Peter F. Lebowitz, M.D., Ph.D., Global Oncology Head, Janssen Research & Development, LLC. “We are only starting to uncover the full potential of this compound, and we remain committed to the continued study of daratumumab to more fully understand its utility for patients with multiple myeloma and other cancer types.”

Overall, the safety of the DARZALEX combination therapy was consistent with the known safety profiles of DARZALEX monotherapy (D) and lenalidomide plus dexamethasone (Rd), respectively. In data from the POLLUX trial, the most frequent (≥20 percent) adverse reactions (ARs) [DRd/Rd] were infusion reactions (48 percent/0 percent), diarrhea (43 percent/25 percent), nausea (24 percent/14 percent), fatigue (35 percent/28 percent), pyrexia (20 percent/11 percent), upper respiratory tract infection (65 percent/51 percent), muscle spasms (26 percent/19 percent), cough (30 percent/15 percent) and dyspnea (21 percent/12 percent).¹ The overall incidence of serious ARs was 49 percent (DRd) compared with 42 percent (Rd).¹ Serious ARs (Grade 3/4) – which had at least a 2 percent greater incidence in the DRd arm compared to the Rd arm – were pneumonia (12 percent/10 percent), upper respiratory tract infection (7 percent/4 percent), influenza (3 percent/1 percent) and pyrexia (3 percent/1 percent).¹ Seven percent/8 percent of patients discontinued therapy due to an AR.¹ The most common treatment-emergent hematology laboratory abnormalities [DRd/Rd] were lymphopenia (95 percent/87 percent), neutropenia (92 percent/87 percent), thrombocytopenia (73 percent/67 percent) and anemia (52 percent/57 percent).¹ The most common Grade 3/4 treatment-emergent hematology laboratory abnormalities were neutropenia (53 percent/40 percent), lymphopenia (52 percent/38 percent), thrombocytopenia (13 percent/15 percent) and anemia (13 percent/19 percent).¹

In data from the CASTOR study, the safety of the DARZALEX combination therapy was consistent with the known safety profiles of DARZALEX monotherapy (D) and bortezomib plus dexamethasone (Vd),
respectively. The most frequent ARs [DVd/Vd] (>20 percent) were infusion reactions (45 percent/0 percent), diarrhea (32 percent/22 percent), peripheral edema (22 percent/13 percent), upper respiratory tract infection (44 percent/30 percent), peripheral sensory neuropathy (47 percent/38 percent), cough (27 percent/14 percent) and dyspnea (21 percent/11 percent).\textsuperscript{1} The overall incidence of serious ARs was 42 percent (DVd) compared with 34 percent (Vd).\textsuperscript{1} Serious ARs (Grade 3/4) – which had at least a 2 percent greater incidence in the DVd arm compared to the Vd arm – included upper respiratory tract infection (5 percent/2 percent), diarrhea (2 percent/0 percent) and atrial fibrillation (2 percent/0 percent).\textsuperscript{1} Seven percent/9 percent of patients discontinued therapy due to an AR.\textsuperscript{1} The most common treatment-emergent hematology laboratory abnormalities were thrombocytopenia (90 percent/85 percent), lymphopenia (89 percent/81 percent), neutropenia (58 percent/40 percent) and anemia (48 percent/56 percent).\textsuperscript{1} The most common Grade 3/4 treatment-emergent hematology laboratory abnormalities were lymphopenia (48 percent/27 percent), thrombocytopenia (47 percent/35 percent), neutropenia (15 percent/6 percent) and anemia (13 percent/14 percent).\textsuperscript{1}

The recommended dose of DARZALEX is 16 mg/kg body weight administered as an intravenous infusion.\textsuperscript{1} The dosing schedule for DARZALEX in combination with lenalidomide and dexamethasone begins with weekly administration (weeks 1-8) and reduces in frequency over time to every two weeks (weeks 9-24) and ultimately every four weeks (week 25 onwards) until disease progression.\textsuperscript{1} The dosing schedule for DARZALEX in combination with bortezomib and dexamethasone begins with weekly administration (weeks 1-9) and reduces in frequency over time to every three weeks (weeks 10-24) and ultimately every four weeks (weeks 25 and onwards) until disease progression.\textsuperscript{1}

In August 2012, Janssen Biotech, Inc. and Genmab A/S entered a worldwide agreement, which granted Janssen an exclusive license to develop, manufacture and commercialize DARZALEX.\textsuperscript{9} DARZALEX is commercialized in the U.S. by Janssen Biotech, Inc. For the full Prescribing Information, please visit www.DARZALEX.com.\textsuperscript{9}

**About DARZALEX® (daratumumab) Injection, for Intravenous Infusion**

DARZALEX\textsuperscript{®} (daratumumab) injection for intravenous use is the first CD38-directed cytolytic antibody approved anywhere in the world.\textsuperscript{6} CD38 is a surface protein that is highly expressed across multiple myeloma cells, regardless of disease stage.\textsuperscript{10} DARZALEX is believed to induce tumor cell death through multiple immune-mediated mechanisms of action, including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), as well as through apoptosis, in which a series of molecular steps in a cell lead to its death.\textsuperscript{1} A subset of myeloid derived suppressor cells (MDSCs), CD38+ regulatory T cells (Tregs) and CD38+ B cells (Bregs) were decreased by DARZALEX.\textsuperscript{1} DARZALEX is being evaluated in a comprehensive clinical development program that includes five Phase 3 studies across a range of treatment settings in multiple
myeloma, such as in frontline and relapsed settings. Additional studies are ongoing or planned to assess its potential for a solid tumor indication and in other malignant and pre-malignant diseases in which CD38 is expressed, such as smoldering myeloma and non-Hodgkin's lymphoma. DARZALEX was the first cytolytic antibody to receive regulatory approval to treat relapsed or refractory multiple myeloma.

**About Multiple Myeloma**

Multiple myeloma is an incurable blood cancer that occurs when malignant plasma cells grow uncontrollably in the bone marrow. Refractory cancer occurs when a patient's disease is resistant to treatment or in the case of multiple myeloma, patients progress within 60 days of their last therapy. Relapsed cancer means the disease has returned after a period of initial partial or complete remission. Globally, it is estimated that 124,225 people were diagnosed and 87,084 died from the disease in 2015. While some patients with multiple myeloma have no symptoms at all, most patients are diagnosed due to symptoms which can include bone fracture or pain, low red blood counts, fatigue, calcium elevation, kidney problems or infections.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS** - None

**WARNINGS AND PRECAUTIONS**

**Infusion Reactions** – DARZALEX can cause severe infusion reactions. Approximately half of all patients experienced a reaction, most during the first infusion. 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 for life-threatening (Grade 4) reactions. 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 – In patients who received Darzalex in combination with lenalidomide and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: neutropenia (92%), thrombocytopenia (73%), 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 were pneumonia (12%), upper respiratory tract infection (7%), influenza (3%) and pyrexia (3%).

In patients who received Darzalex in combination with bortezomib and dexamethasone, the most frequently reported adverse reactions (incidence ≥20%) were: thrombocytopenia (90%), neutropenia (58%), 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 were upper respiratory tract infection (5%), diarrhea (2%) and atrial fibrillation (2%).

In patients who received Darzalex as monotherapy, the most frequently reported adverse reactions (incidence ≥20%) were: neutropenia (60%), thrombocytopenia (48%), infusion reactions (48%), fatigue (39%), nausea (27%), back pain (23%), pyrexia (21%), cough (21%), and upper respiratory tract infection (20%). Serious adverse reactions were reported in 51 (33%) patients. The most frequent serious adverse reactions were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%).

DRUG INTERACTIONS

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

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

About the Janssen Pharmaceutical Companies

At the Janssen Pharmaceutical Companies of Johnson & Johnson, we are working to create a world without disease. Transforming lives by finding new and better ways to prevent, intercept, treat and cure disease inspires us. We bring together the best minds and pursue the most promising science. We are Janssen. We collaborate with the world for the health of everyone in it. Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenUS and www.twitter.com/JanssenGlobal.

This press release contains “forward-looking statements” as defined in the Private Securities Litigation Reform Act of 1995 regarding DARZALEX’s potential and further development of daratumumab. 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 Biotech, Inc., Janssen Research & Development, LLC and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges inherent in product research and development, including the uncertainty of clinical success and obtaining regulatory approvals; uncertainty of commercial success for new products or new indications; manufacturing difficulties or delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and description of these risks, uncertainties and other factors can be found in Johnson & Johnson’s Annual Report on Form 10-K for the fiscal year ended January 3, 2016, including in Exhibit 99 thereto, 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 or Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.