# CHMP Issues Positive Opinion Recommending DARZALEX® (daratumumab) for Relapsed and Refractory Multiple Myeloma

## Company Announcement

- **CHMP issued positive opinion for DARZALEX for relapsed and refractory multiple myeloma**
- **Final decision from European Commission expected in the coming months**

**Copenhagen, Denmark; April 1, 2016 – Genmab A/S (Nasdaq Copenhagen: GEN) announced today that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has issued a positive opinion recommending the grant of a conditional marketing authorization for DARZALEX® (daratumumab) in the European Union.** The recommendation is for the use of DARZALEX as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor (PI) and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

The positive opinion of the CHMP was predominantly based on data from the Phase II study (SIRIUS MMY2002, published in *The Lancet* in January 2016) of daratumumab in multiple myeloma patients who have received at least three prior lines of therapy including both a PI and an immunomodulatory agent, or who are double refractory to a PI and an immunomodulatory agent. Additional data from four other studies, including the Phase I/II GEN501 monotherapy study (published in *The New England Journal of Medicine* in August 2015) support the opinion. In August 2012, Genmab granted Janssen Biotech, Inc. an exclusive worldwide license to develop, manufacture and commercialize daratumumab.

"We are very pleased to receive the positive opinion from the CHMP for the use of DARZALEX as monotherapy in patients with relapsed and refractory multiple myeloma. The CHMP opinion brings Genmab and its partner Janssen one step closer towards offering a fundamentally new treatment option to patients with multiple myeloma in Europe, and we look forward to the decision of the European Commission," said Jan van de Winkel, Ph.D., Chief Executive Officer of Genmab.

A CHMP opinion is one of the final steps in the regulatory process of the European Medicines Agency. The CHMP reviewed DARZALEX under the EMA's accelerated assessment program. A final decision by the European Commission is anticipated in 60 – 90 days.

In November 2015, DARZALEX was approved by the U.S. FDA under a Breakthrough Therapy Designation and Priority Review for the treatment of 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 an immunomodulatory agent.

**Safety and Efficacy Data from the Phase II MMY2002 (SIRIUS) Study**
Results from the pivotal Phase II SIRIUS study showed that treatment with single-agent DARZALEX resulted in an overall response rate (ORR) of 29.2% in patients who had received a median of five prior lines of therapy, including a PI and an immunomodulatory agent. Stringent complete response (sCR) was reported in 2.8% of patients, very good partial response (VGPR) was reported in 9.4% of patients, and partial response (PR) was reported in 17% of patients.[1]

For responders, the median duration of response was 7.4 months. At baseline, 97% of patients were refractory to their last line of therapy, 95% were refractory to both a PI and an immunomodulatory agent, and 77% were refractory to alkylating agents.[1]

The warnings and precautions for DARZALEX include infusion-related reactions (IRRs) and interference with serological testing.[1] The most commonly occurring adverse reactions (in 20 percent or more of patients in three pooled clinical studies) were IRRs, fatigue, nausea, back pain, anemia, neutropenia

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(abnormally low levels of neutrophils, a type of white blood cell) and thrombocytopenia (abnormally low levels of platelets in the blood).[1]

In data from three pooled clinical studies including a total of 156 patients, four percent of patients discontinued treatment due to adverse reactions, none of which were considered drug-related. IRRs were reported in approximately half of all patients treated with DARZALEX, the majority of which (91 percent) occurred during the first infusion. Seven percent of patients had an IRR at more than one infusion. Common (≥5 percent) symptoms of IRRs included nasal congestion, chills, cough, allergic rhinitis, throat irritation, dyspnea, and nausea, and these were mild to moderate in severity.[1] Severe IRRs (4 percent), including bronchospasm (1.3 percent), hypertension (1.3 percent), and hypoxia, or decreased oxygen supply to the tissues (0.6 percent), were also reported.[1]

**About multiple myeloma**
Multiple myeloma is an incurable blood cancer that starts in the bone marrow and is characterized by an excess proliferation of plasma cells.[2] Multiple myeloma is the third most common blood cancer in the U.S., after leukemia and lymphoma.[3] Approximately 26,850 new patients were estimated to be diagnosed with multiple myeloma and approximately 11,240 people would die from the disease in the U.S. in 2015.[4] Globally, it was estimated that 124,225 people would be diagnosed and 87,084 would die from the disease in 2015.[5] While some patients with multiple myeloma have no symptoms at all, most patients are diagnosed due to symptoms which can include bone problems, low blood counts, calcium elevation, kidney problems or infections.[6] Patients who relapse after treatment with standard therapies, including proteasome inhibitors or immunomodulatory agents, have poor prognoses and few treatment options.[7]

**About DARZALEX® (daratumumab)**
DARZALEX® (daratumumab) injection for intravenous infusion is indicated in the United States for the treatment of 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.[1] DARZALEX is the first monoclonal antibody (mAb) to receive U.S. Food and Drug Administration (FDA) approval to treat multiple myeloma. For more information, visit www.DARZALEX.com.

Daratumumab is a human IgG1k monoclonal antibody (mAb) that binds with high affinity to the CD38 molecule, which is highly expressed on the surface of multiple myeloma cells. It is believed to induce rapid tumor cell death through programmed cell death, or apoptosis,[1,8] and multiple immune-mediated mechanisms, including complement-dependent cytotoxicity,[1,8] antibody-dependent cellular phagocytosis[9,10] and antibody-dependent cellular cytotoxicity.[1,8] In addition, daratumumab therapy results in a reduction of immune-suppressive myeloid derived suppressor cells (MDSCs) and subsets of regulatory T cells (Tregs) and B cells (Bregs), all of which express CD38. These reductions in MDSCs, Tregs and Bregs were paralleled by increases in CD4+ and CD8+ T cell numbers in both the peripheral blood and bone marrow.[1]

Daratumumab is being developed by Janssen Biotech, Inc. under an exclusive worldwide license to develop, manufacture and commercialize daratumumab from Genmab. Five Phase III clinical studies with daratumumab in relapsed and frontline settings are currently ongoing, and additional studies are ongoing or planned to assess its potential in other malignant and pre-malignant diseases on which CD38 is expressed, such as smoldering myeloma and non-Hodgkin's lymphoma.

**About Genmab**
Genmab is a publicly traded, international biotechnology company specializing in the creation and development of differentiated antibody therapeutics for the treatment of cancer. Founded in 1999, the

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company has two approved antibodies, Arzerra® (ofatumumab) for the treatment of certain chronic lymphocytic leukemia indications and DARZALEX® (daratumumab) for the treatment of heavily pretreated or double refractory multiple myeloma. Daratumumab is in clinical development for additional multiple myeloma indications and for non-Hodgkin's lymphoma. Genmab also has a broad clinical and pre-clinical product pipeline. Genmab's technology base consists of validated and proprietary next generation antibody technologies - the DuoBody® platform for generation of bispecific antibodies, and the HexaBody® platform which creates effector function enhanced antibodies. The company intends to leverage these technologies to create opportunities for full or co-ownership of future products. Genmab has alliances with top tier pharmaceutical and biotechnology companies. For more information visit www.genmab.com.

**Contact:**
Rachel Curtis Gravesen, Senior Vice President, Investor Relations & Communications
T: +45 33 44 77 20; M: +45 25 12 62 60; E: r.gravesen@genmab.com

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[1] DARZALEX Prescribing Information, November 2015.
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[7] Kumar, SK et al. Risk of progression and survival in multiple myeloma relapsing after last therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. Leukemia. 2012; 26:149-57.
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[9] Overjijk MB, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. MAbs. 2015;7:311-21.
[10] Khagi and Mark. Potential role of daratumumab in the treatment of multiple myeloma. Onco Targets Ther. 2014; 7: 1095–1100.