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## Major independent trial demonstrates significant anticancer benefit of Zometa® in women with early-stage breast cancer

- *Zometa when added to hormone therapy, following surgery, significantly reduced the risk of cancer returning or death by 36% beyond clinical benefits achieved with hormone therapy alone<sup>1</sup>*
- *Findings may allow clinicians to improve standard of care for premenopausal women diagnosed with hormone-sensitive, early-stage breast cancer*
- *These are the first data from a large clinical program exploring the direct anticancer effect of Zometa in breast, lung and prostate cancer*

Basel, May 31, 2008 — New data presented today showed that Zometa® (zoledronic acid) offered a significant anticancer benefit for premenopausal women with hormone-sensitive, early-stage breast cancer. The study found that Zometa when added to hormone therapy, following surgery, significantly reduced the risk of cancer returning or death by 36% beyond clinical benefits achieved with hormone therapy alone.

Investigators from the Austrian Breast & Colorectal Cancer Study Group (ABCSCG) announced the findings during a plenary presentation today at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago, Illinois, USA.

“This study is the first large-scale trial to demonstrate the significant antitumor benefit of zoledronic acid,” said lead investigator Michael Gnant, M.D., of the Medical University of Vienna. “These new findings may allow oncologists to further improve the standard of care for premenopausal women with hormone-sensitive breast cancer.”

According to the World Health Organization (WHO), each year approximately 500,000 women die worldwide because their breast cancer has returned or spread<sup>2</sup>. Moreover, the incidence of breast cancer has been rising in recent decades<sup>3</sup>.

“These results represent a tremendous advance for women hoping to prevent the return of their cancer,” said David Epstein, President and CEO of Novartis Oncology. “We continue to explore the anticancer benefit of Zometa in a large clinical program with nearly 20,000 patients in 10 trials worldwide. We anticipate additional results over the next two to three years.”

The ABCSCG-12 study, in which women were treated for three years and observed for an additional two years, demonstrated that the addition of Zometa to hormone therapy (tamoxifen or anastrozole) significantly prolonged both disease-free survival and recurrence-free survival. With Zometa, the risk of disease-free survival events (which include death from any cause) fell by 36% (P=0.01), compared to hormone therapy alone. Furthermore, the risk of recurrence-free survival events fell by 35% (P=0.015) with Zometa, compared to hormone therapy alone. A positive but non-significant trend toward an overall survival benefit was also seen in patients who received Zometa<sup>1</sup>.

Zometa is the world's leading treatment for the prevention or delay of skeletal-related events (SREs) in patients with advanced malignancies involving bone across a broad range of tumors. Laboratory research had suggested that Zometa may also help protect patients from the spread of cancer to other parts of the body (distant metastatic sites) and help keep patients recurrence-free.

Zometa slows the bone-destroying effect that occurs with bone metastases by fighting abnormal activation of osteoclasts, cells that normally break down old bone, and osteoblasts, cells that normally build new bone. Growth factors produced by cancer cells overstimulate osteoclasts and osteoblasts, causing excessive erosion of bone and/or the abnormal buildup of new but unstable bone.

Laboratory research has suggested that Zometa may also have anticancer effects, including helping to protect against the return and spread of cancer before it reaches an advanced stage. A tumor passes through six stages on its path to metastasizing (spreading). In the laboratory, Zometa has been shown to make passage through these stages more difficult by inhibiting angiogenesis (formation of blood vessels that grow and feed cancer cells), stimulating cancer-fighting T-cells, inducing tumor cell apoptosis (programmed cell death) and increasing the activity of anticancer agents that target tumor cell metastases<sup>4</sup>.

A growing number of clinical studies are examining the potential anticancer impact of Zometa. One of the largest of these studies, AZURE (Adjuvant Zoledronic acid to redUce REcurrence), has completed enrollment. The study will evaluate the impact of Zometa in reducing risk of cancer recurrence in 3,360 premenopausal and postmenopausal women with Stage II/III breast cancer.

Another study presented at this year's ASCO meeting evaluated the effect of Zometa on bone marrow micrometastases. The study was conducted in 120 premenopausal and postmenopausal women with Stage II/III breast cancer undergoing treatment pre- and post-surgery. For those women who were negative for disseminated cancer cells at baseline, significantly more women who took Zometa in addition to chemotherapy remained negative for disseminated cancer cells over time.

### **Study details**

The Austrian Breast & Colorectal Cancer Study Group Trial 12 (ABCSCG-12) is an open-label, multicenter, Phase III study that enrolled 1,803 premenopausal women with estrogen-receptor-positive Stage I or II breast cancer, with fewer than 10 axillary lymph nodes involved. Patients were recruited for the study after curative surgery and initiation of goserelin treatment for ovarian suppression, and randomly assigned into one of four study groups: (1) anastrozole plus Zometa; (2) anastrozole alone; (3) tamoxifen plus Zometa; (4) tamoxifen alone. The treatment period was three years and the median follow-up period was an additional two years<sup>1</sup>.

The primary endpoint of the study was disease-free survival for all four study groups. Recurrence-free survival, overall survival, and safety were secondary endpoints. (Disease-free survival was defined as the length of time after randomization during which patients had no local recurrence, contralateral breast cancer, distant metastasis, secondary carcinoma, and/or death from any cause. Recurrence-free survival was defined as the length of time after randomization during which patients had no local recurrence, contralateral breast cancer, distant metastasis, and/or secondary carcinoma.) Exploratory endpoints included bone-metastases-free survival<sup>1</sup>.

At the median follow-up of five years, disease-free survival events were reduced by 36% (P=0.01) with Zometa and the risk of recurrence-free survival events fell by 35% (P=0.015) versus hormone therapy alone. Sixteen deaths had occurred among patients who received Zometa with hormone therapy versus 26 deaths in patients who received hormone therapy

alone, which resulted in a nonsignificant reduction in the risk of death in patients who received Zometa compared with those who received hormone therapy alone (P=0.103). A similar trend was noted toward a reduction in bone metastases among patients who received Zometa compared with those who received hormone therapy alone (16 versus 23). Longer follow-up and a larger number of events will be necessary to determine if any significant differences exist between the groups for overall survival and bone-metastases-free survival. Overall, treatment was generally well-tolerated and side effects were consistent with known drug safety profile<sup>1</sup>.

### **About Zometa**

Zometa is indicated for the treatment of prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumor-induced hypercalcemia) in patients with advanced malignancies involving bone. Zometa is approved and indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. An intravenous bisphosphonate, Zometa is the only therapy to demonstrate efficacy in reducing or delaying bone complications across a broad range of tumor types such as breast, prostate, lung and renal cell cancers in patients with metastatic disease when administered monthly. Zometa offers patients, nurses and clinicians a convenient 4 mg, 15-minute infusion.

### **Important safety information**

In clinical studies, the safety profile with Zometa was similar to that of pamidronate. Zometa has been associated with reports of renal insufficiency. Patients should have serum creatinine assessed prior to receiving each dose of Zometa. Caution is advised when Zometa is used in aspirin-sensitive patients, or with aminoglycosides, loop diuretics, and other potentially nephrotoxic drugs. Due to the risk of clinically significant deterioration in renal function, single doses of Zometa should not exceed 4 mg and the duration of infusion should be no less than 15 minutes in 100 ml of diluent.

In clinical trials in patients with bone metastases and hypercalcemia of malignancy (HCM), Zometa had a safety profile similar to other intravenous bisphosphonates. The most commonly reported adverse events included flu-like syndrome (fever, arthralgias, myalgias, skeletal pain), fatigue, gastrointestinal reactions, anemia, weakness, cough, dyspnea and edema. Zometa should not be used during pregnancy. Zometa is contraindicated in patients with clinically significant hypersensitivity to zoledronic acid or other bisphosphonates, or any of the excipients in the formulation of Zometa.

**Osteonecrosis of the Jaw (ONJ):** ONJ has been reported in patients with cancer receiving treatment including bisphosphonates, chemotherapy, and/or corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors. While on treatment, these patients should avoid invasive dental procedures if possible. No data are available to suggest whether discontinuation of bisphosphonate therapy reduces the risk of ONJ in patients requiring dental procedures.

Please see full Prescribing Information.

### **Disclaimer**

The foregoing release contains forward-looking statements that can be identified by terminology such as “may”, “continue to”, “anticipate”, “potential”, “will”, or similar expressions, or by express or implied discussions regarding potential new indications or labelling for Zometa or regarding potential future revenues from Zometa. Such forward-looking statements reflect the current views of the Company regarding future events, and involve known and unknown risks, uncertainties and other factors that may cause actual

results with Zometa to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that Zometa will be submitted or approved for any additional indications or labelling in any market. Nor can there be any guarantee that Zometa will achieve any particular levels of revenue in the future. In particular, management's expectations regarding Zometa could be affected by, among other things, unexpected regulatory actions or delays or government regulation generally; unexpected clinical trial results, including unexpected new clinical data and unexpected additional analysis of existing clinical data; the company's ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; government, industry and general public pricing pressures, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated or expected. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

### **About Novartis**

Novartis AG provides healthcare solutions that address the evolving needs of patients and societies. Focused solely on growth areas in healthcare, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic pharmaceuticals, preventive vaccines and diagnostic tools, and consumer health products. Novartis is the only company with leading positions in these areas. In 2007, the Group's continuing operations (excluding divestments in 2007) achieved net sales of USD 38.1 billion and net income of USD 6.5 billion. Approximately USD 6.4 billion was invested in R&D activities throughout the Group. Headquartered in Basel, Switzerland, Novartis Group companies employ approximately 98,000 full-time associates and operate in over 140 countries around the world. For more information, please visit <http://www.novartis.com>.

### **For more information**

Additional information regarding Zometa and Novartis Oncology can be found on the websites <http://www.novartisoncologyvpo.com/ZOMETA>, [www.zometa.com](http://www.zometa.com) and [www.novartisoncology.com](http://www.novartisoncology.com).

### **References**

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