

NOVARTIS AG  
Form 6-K  
December 31, 2002

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# SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

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## FORM 6-K

REPORT OF FOREIGN PRIVATE ISSUER  
Pursuant to Rule 13a-16 or 15d-16 of  
the Securities Exchange Act of 1934

Report on Form 6-K for the month of December 2002

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## Novartis AG

(Name of Registrant)

Lichtstrasse 35  
4056 Basel  
Switzerland

(Address of Principal Executive Offices)

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Indicate by check mark whether the registrant files or will file annual reports under cover of Form 20-F or Form 40-F.

Form 20-F       Form 40-F

Indicate by check mark whether the registrant by furnishing the information contained in this form is also thereby furnishing the information to the Commission pursuant to Rule 12g3-2(b) under the Securities Exchange Act of 1934.

Yes       No

Enclosures:

1. Glivec gains FDA approval for first-line treatment of chronic myeloid leukemia
2. Novartis submits filing of Foradil® Certihaler in US and EU
3. Novartis files a supplemental new drug application for Starlix®
4. Novartis and Genentech submit amendment to the Biologics License Application for Xolair® to FDA
5. FDA approves Clozaril® to treat suicidal behavior in patients with schizophrenia and schizoaffective disorder
6. Trileptal® shows efficacy for continuous seizure control in long-term management of epilepsy
7. Zometa® better than pamidronate in reducing risk of bone complications of advanced breast cancer, according to data presented at major medical meeting

8. Novartis Distinguished Scientist Awards and Leading Scientist Awards 2002
  9. Study suggests Exelon® effective in patients with mixed dementia
  10. Novartis Launches Z-FAST: A Study Evaluating Femara® and Zometa® in Postmenopausal Women with Early Breast Cancer
  11. New longer-term data show Glivec nine times more likely than interferon combination to achieve chronic myeloid leukemia key treatment goal
  12. Investigational oral drug from Novartis demonstrated favorable results in patients with excess iron from transfusion-dependent anemias; new data featured at major US medical meeting
  13. Glivec® (imatinib) approved in Switzerland for first-line treatment of adults and children with chronic myeloid leukemia (CML), allowing broader, earlier use
  14. Novartis completes Health & Functional Food divestment to Associated British Foods
  15. Novartis initiates largest global clinical trial of Zelmac® in IBS
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#### **Investor Relations Release**

#### **Glivec gains FDA approval for first-line treatment of chronic myeloid leukemia**

*Action paves the way for earlier use; Glivec delays progression of disease to advanced stages; approval marks third indication in less than 19 months*

Basel, 21 December 2002 Novartis announces that the United States Food and Drug Administration (FDA) has approved Glivec® (imatinib)<sup>1</sup> for first-line treatment of patients with newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML). The FDA approval followed a priority review and was based on 12-month data from a large head-to-head study comparing Glivec with a combination of interferon-alpha and cytosine arabinoside (IFN/Ara-C), a traditional treatment for CML. In this study, patients treated with Glivec given orally at 400 mg per day were nine times more likely to achieve a complete cytogenetic response compared with those treated with the IFN/Ara-C combination. In addition, Glivec significantly delayed the time to progression to the more advanced stages of CML.

Novartis also has submitted marketing applications with health authorities in the EU, seeking marketing authorization for Glivec for the first-line treatment of newly diagnosed adults and children with Ph+ CML. On 20 September 2002, Glivec received a positive opinion from the Committee for Proprietary Medicinal Products (CPMP) of the EU for this indication.

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"Studies have shown that response rates to Glivec are higher when therapy is initiated earlier in the course of the disease. This approval allows newly diagnosed patients earlier access to Glivec when the potential benefits from the drug are greatest," said David Epstein, President, Novartis Oncology.

### Clinical data

The 12-month data used to support the approval were from the International Randomized Study of Interferon vs. STI571 (IRIS) a head-to-head study comparing the efficacy of Glivec with the combination therapy of IFN, a biologic, and Ara-C, a chemotherapy agent. Updated 18-month data were presented 8 December 2002 at the annual meeting of the American Society of Hematology (ASH) in Philadelphia, Pennsylvania. The updated 18-month data have not been reviewed by the health authorities.

<sup>1</sup> In the US: Gleevec (imatinib mesylate).

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*Following are comparative statistics:*

IRIS Study	12-month data submitted to health authorities (28 June 2002)*		Updated 18-month data presented at ASH (8 December 2002)	
	Glivec Arm	IFN/Ara-C Arm	Glivec Arm	IFN/Ara-C Arm
Complete**				
Cytogenetic Response <sup>(1)</sup>	68%	7%	74%	8%
Major***				
Cytogenetic Response <sup>(2)</sup>	83%	20%	85%	22%
Progression-Free Survival	97.2%	80.3%	92.3%	73.6%

\* responses were confirmed by subsequent assessment in most cases.

\*\* no cells detected containing the Ph+ chromosome.

\*\*\* detection of less than 35% Ph+ cells remaining.

(1) FDA references 54% and 3% on Glivec and IFN/Ara-C arms, respectively (12-month).

(2) FDA references 76% and 12% on Glivec and IFN/Ara-C arms, respectively (12-month).

Based on the 12-month data filed with the health authorities, only 2% and 0.7% of patients in the Glivec arm withdrew from the study or crossed over to the IFN/Ara-C arm for tolerability reasons, respectively. In contrast 6% and 23% of patients, respectively, in the IFN/Ara-C arm withdrew from the study or crossed over for tolerability reasons.

### Glivec

In most countries in which it is approved, Glivec is indicated for the treatment of patients with Ph+ CML in the blast crisis, accelerated phase or in chronic phase after failure of interferon-alpha therapy. In February 2002, just nine months following the initial CML approval, Glivec received FDA approval for the treatment of patients with Kit (CD 117) positive unresectable (inoperable) and/or metastatic malignant gastrointestinal stromal tumors (GISTs). The GIST indication also was approved on 24 May 2002 in the EU.

### Contraindications and adverse events

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In the first-line study (IRIS), the safety profile with Glivec at the 12-month follow-up was similar to that of previous Phase II studies in other CML patients. The majority of patients treated with Glivec experienced adverse events at some time. Most events were of mild to moderate grade and treatment was discontinued for adverse events only in 2% of patients in chronic phase, 3% in accelerated phase and 5% in blast crisis. The most common side effects included nausea, fluid retention, vomiting, diarrhea, hemorrhage, muscle cramps, skin rash, fatigue, headache, dyspepsia and dyspnea, as well as neutropenia and thrombocytopenia.

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The foregoing release contains forward-looking statements that can be identified by statements of expectations or future events, or by express or implied discussions regarding potential additional revenues to Novartis as a result of this new indication for Glivec, potential approvals of additional indications for Glivec in other markets, or regarding the long-term impact of a patient's use of Glivec. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results with Glivec to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that the approval described above will result in any additional revenues to Novartis, that additional indications for Glivec will be approved in other markets, or regarding the long-term impact of a patient's use of Glivec. In particular, management's expectations regarding Glivec could be affected by, among other things, additional analysis of Glivec clinical data; new clinical data; unexpected clinical trial results; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; and other risks and factors referred to in the Company'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 AG (NYSE: NVS) is a world leader in pharmaceuticals and consumer health. In 2001, the Group's businesses achieved sales of CHF 32.0 billion (USD 19.1 billion) and a net income of CHF 7.0 billion (USD 4.2 billion). The Group invested approximately CHF 4.2 billion (USD 2.5 billion) in R&D. Headquartered in Basel, Switzerland, Novartis Group companies employ about 74 000 people and operate in over 140 countries around the world. For further information please consult <http://www.novartis.com>.

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Additional information on Novartis Oncology and Glivec can be found at [www.novartisoncology.com](http://www.novartisoncology.com) or [www.glivec.com](http://www.glivec.com). Additional media information can be found at [www.novartisoncologyvpo.com](http://www.novartisoncologyvpo.com).

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### MEDIA RELEASE COMMUNIQUE AUX MEDIAS MEDIENMITTEILUNG

#### Novartis submits filing of Foradil® Certihaler in US and EU

*New-generation delivery system employs multi-dose dry powder inhaler technology*

Basel, 20 December 2002 Novartis today announced the submission of a New Drug Application (NDA) to the US Food and Drug Administration (FDA) and health authorities in the EU for Foradil® Certihaler (formoterol fumarate inhalation powder).

Foradil Certihaler employs a novel, breath-activated multi-dose dry powder inhaler (MDDPI) technology, developed by SkyePharma Plc, that gives patients confirmation that the full dose of medication has been taken.

"The submission of a New Drug Application for Foradil Certihaler is an important step in the evolution of the Foradil line," said Joerg Reinhardt, Head of Development, Novartis Pharma AG. "We anticipate that this product will prove to be a valuable option for asthma patients who require maintenance therapy with a long-acting bronchodilator."

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In October, Novartis granted Schering-Plough exclusive US distribution and marketing rights to all Foradil products. Schering-Plough currently markets Foradil® Aerolizer (formoterol fumarate inhalation powder). Novartis retains international rights to the Foradil product line. Novartis licensed Formoterol from Yamanouchi in 1987. SkyePharma will manufacture and supply the Foradil Certihaler to Novartis.

The foregoing press release contains forward-looking statements that can be identified by forward-looking terminology such as "anticipate", "will manufacture" or similar expressions, or by express or implied discussions regarding the potential that the New Drug Application described above will be approved, or regarding potential revenues from future sales of the Foradil Certihaler. Such statements involve known and unknown risks, uncertainties and other factors that may cause the actual results to be materially different from any future results, performance, or achievements expressed or implied by such statements. There are no guarantees that the New Drug Application for the Foradil Certihaler will be approved, or that it will result in any additional sales of Foradil or of any sales of Certihaler. Any such approval, sales or other results can be affected by, amongst other things, uncertainties relating to product efficacy, regulatory actions or delays or government regulation generally, the ability to obtain or maintain patent or other proprietary intellectual property protection and competition in general, as well as factors discussed in Novartis AG's Form 20-F filed with the Securities and Exchange Commission. Any of these and other factors can cause the actual results to differ materially from the expected or predicted results.

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### Investor Relations Release

#### Novartis files a supplemental new drug application for Starlix®

*Combination therapy with a thiazolidinedione would provide new option for controlling and maintaining blood sugar levels in type 2 diabetes patients*

Basel, 20 December 2002 Novartis announced it has filed a supplemental new drug application (sNDA) for Starlix® (nateglinide) for use in combination with a thiazolidinedione (TZD), a commonly used class of oral antidiabetic agents. The FDA submission is based on the findings of a 24-week study involving 402 patients with type 2 diabetes. Starlix is already indicated in combination with metformin for treatment of type 2 diabetes.

Starlix works by stimulating rapid, short-acting insulin secretion that reduces the mealtime increase in blood glucose levels and effectively lowers overall blood glucose levels. Thiazolidinediones (TZDs) improve insulin sensitivity and help control blood sugar by reducing fasting plasma glucose levels. By using Starlix in combination with a TZD, both the mealtime and fasting glucose levels will be managed, and could potentially lead to substantial reductions in HbA<sub>1c</sub>.

#### About the study

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The FDA submission is based on the positive findings of a 24-week multicentre double-blind randomized study which compared the efficacy of Starlix (120 mg, taken before a meal) and placebo added to ongoing open label rosiglitazone (Avandia® 8 mg, q.d.) in 402 patients with type 2 diabetes who had not reached target HbA<sub>1c</sub> levels on rosiglitazone alone (HbA<sub>1c</sub> 7 percent 11 percent).

The study found that in patients randomized to the Starlix/rosiglitazone combination, HbA<sub>1c</sub> decreased from 8.3 percent to 7.5 percent, but in the placebo-treated patients, HbA<sub>1c</sub> did not change. Target HbA<sub>1c</sub> (less than 7 percent) was achieved by 38 percent of patients treated with the combination therapy and by 9 percent of patients remaining on rosiglitazone monotherapy.

The study also found that in the Starlix/rosiglitazone combination patients, fasting plasma glucose decreased by 0.7 mmol/L, 2-hr post prandial glucose decreased by 2.7 mmol/L and 30-minute insulin levels increased by 165 pmol/L compared to no changes from baseline of these parameters with placebo added to rosiglitazone ( $p < 0.001$ ).

In this study, the overall safety, tolerability and effects on lipid parameters were similar in the two treatment groups. However, the incidence of confirmed hypoglycemia in the group treated with combination therapy (PG < 2.8 mmol/L) was 4.5 percent (*versus* 0% hypoglycemia in the control group).

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### About Starlix

Starlix was approved in the United States in 2001 as monotherapy for newly diagnosed or drug-naïve patients with type 2 diabetes and as an add-on therapy for people with type 2 diabetes who are being treated with metformin, a leading oral antidiabetic agent. Starlix has an excellent safety and tolerability profile across all clinical trials. Starlix is also approved in many countries around the world for the treatment of type 2 diabetes. Nateglinide is licensed to Novartis Pharma AG from Ajinomoto Co., Inc.

This press release contains forward looking statements which can be identified by the use of forward-looking terminology such as "would provide", "will be", "could potentially be", or similar expressions, or by express or implied discussions regarding potential additional indications for Starlix, or potential additional revenue to Novartis from Starlix sales. Such forward looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. There are no guarantees that the aforementioned clinical trial will result in any additional indications for Starlix in any market, or in any additional revenue to Novartis from Starlix sales. Any such results can be affected by, amongst other things, uncertainties relating to product development, including uncertainties regarding the outcome of clinical trials, regulatory actions or delays or government regulation generally, the ability to obtain or maintain patent or other proprietary intellectual property protection and competition in general, as well as factors discussed in Novartis AG's Form 20-F filed with the Securities and Exchange Commission. Any of these and other factors can cause the actual results to differ materially from the expected or predicted results.

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**Investor Relations Release**

**Novartis and Genentech submit amendment to the Biologics License Application for Xolair® to FDA**

Basel, 19 December 2002 Novartis announced today the submission to the US Food and Drug Administration (FDA) of an amendment to the application for marketing authorization (Biologics License Application) for Xolair® (omalizumab), a recombinant humanized monoclonal antibody currently under evaluation for the treatment of moderate-to-severe allergic asthma. The submission includes clinical data from more than 6 000 patients, including safety experience from the recently completed ALTO trial with 1 899 patients.

"Submitting the Biologics License Application for Xolair is an important step towards our goal of providing novel biologic treatment options for people struggling to control their asthma," said Thomas Ebeling, CEO of Novartis Pharma AG. "We look forward to continuing our collaboration in this effort with Genentech and with the FDA."

Xolair is a first-in-class monoclonal antibody to IgE in development under an agreement between Novartis Pharma AG, Genentech, Inc. and Tanox, Inc. It is the first agent to specifically target IgE, and if approved, Xolair would be the first biological therapy available for the treatment of asthma in the United States.

Xolair works by binding to circulating IgE and preventing it from attaching to mast cells. Without IgE bound to mast cells, the presence of an allergen will not cause the release of chemical mediators like histamine and leukotrienes, which lead to the symptoms and inflammation of allergic asthma.

Xolair has already received its first marketing license from health authorities in Australia. New data will also be submitted to the European Medical Evaluations Agency (EMA). Novartis expects to resubmit a Xolair marketing application to the EMA in the first half of 2004.

**About Allergic Asthma**

Allergic asthma is the most common form of asthma, a chronic inflammatory disorder of the airways characterized by recurrent episodes of wheezing, breathlessness, chest tightness and coughing that affects approximately 54 million world-wide. In allergic asthma, exposure to an allergen (such as dust, mold or pollen) triggers an allergic cascade, which result in airway obstruction. According to the World Health Organization (WHO) an estimated 180 000 people die from asthma each year worldwide.

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The foregoing press release contains forward-looking statements that can be identified by the use of forward-looking terminology such as "goal toward", "look forward to", "will also be", "expects", or similar expressions, or by express or implied statements regarding the potential for regulatory approvals to market Xolair based on the applications which has been or will be filed. Such forward looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that the aforementioned applications for regulatory approval will result in the commercialisation of Xolair in any market. Any such commercialization, or other results, performance or achievements expressed or implied in such statements, can be affected by, amongst other things, uncertainties relating to product development, including the results of clinical trials, regulatory actions or delays or government regulation generally, uncertainties relating to pharmaceutical production, and the ability to obtain or maintain patent or other proprietary intellectual property protection, as well as factors discussed in Novartis AG's Form 20-F filed with the 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 described herein as anticipated, believed, estimated or expected.

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### **Investor Relations Release**

#### **FDA approves Clozaril® to treat suicidal behavior in patients with schizophrenia and schizoaffective disorder**

*Drug is first ever approved for this indication*

Basel, 19 December 2002 Novartis announced today that it has received approval from the US Food and Drug Administration (FDA) to market Clozaril® (clozapine) for the treatment of recurrent suicidal behavior in patients with schizophrenia and schizoaffective disorder who are at chronic risk. This action by the FDA marks the first time that any medication has been approved for use specifically in treating suicidal behavior. The FDA approval provides for the exclusive marketing of Clozaril for the indication for a period of 36 months. The approval does not apply to the generic formulations of Clozapine.

Novartis filed a supplemental New Drug Application (sNDA) in March 2002, for the indication based upon data from the International Suicide Prevention Trial (InterSePT ), the first study ever to prospectively evaluate a medication in reducing the risk of suicidal behavior.

#### **About suicidal behavior**

Schizophrenia affects up to 24 million people worldwide. Suicide is the leading cause of premature death among patients with schizophrenia and schizoaffective disorder. Overall, these patients have approximately a 40% lifetime risk for suicide attempts and a 10% risk for a completed suicide. Suicidal behavior includes symptoms ranging from having suicidal thoughts, to making suicidal plans and attempting suicide.

#### **About InterSePT**

InterSePT was a multi-center, randomized study initiated in 1998 to compare the efficacy of two antipsychotic compounds, Clozaril and Zyprexa®\* (olanzapine), in reducing the risk of suicidal behavior among patients with schizophrenia or schizoaffective disorder. Clozaril reduced the risk of suicide attempts and hospitalisations to prevent suicide by about 26% compared to Zyprexa. These results were not related to the use of greater concomitant psychotropic medication as Clozaril-treated patients required fewer concomitant psychotropic medications.

Clozaril was originally indicated for the treatment of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug therapies.

The foregoing press release contains forward-looking statements that can be identified by express or implied statements regarding the potential for additional sales of Clozaril in the US as a result of this new indication. Such forward looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results to be materially different from any future results, performance or



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achievements expressed or implied by such statements. There are no guarantees of any additional sales of Clozaril in the US or elsewhere as a result of this new indication. Any such commercial success, or other results, performance or achievements expressed or implied in such statements, can be affected by, amongst other things, competition in general, uncertainties relating to marketing, including uncertainties regarding the potential size of the market for this indication, regulatory actions or delays or government regulation generally, uncertainties relating to pharmaceutical production, and the ability to obtain or maintain patent or other proprietary intellectual property protection, as well as factors discussed in the Company's Form 20-F filed with the 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 described herein as anticipated, believed, estimated or expected.

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Zyprexa® is a trademark of Eli Lilly and Company.

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### Investor Relations Release

#### **Trileptal® shows efficacy for continuous seizure control in long-term management of epilepsy**

*Two-year extension phase of 3 pivotal studies demonstrates reduction in seizure frequency with Trileptal®*

Basel, 11 December 2002 The antiepileptic drug (AED) Trileptal® (oxcarbazepine) demonstrates long term efficacy when used in patients with partial seizures, according to data presented at the 56th annual meeting of the American Epilepsy Society (AES). The two year extension phase of three pivotal studies examined Trileptal as monotherapy or in combination with other AEDs in various epilepsy patient populations. Results were reported from the extension phase of each trial and demonstrated that Trileptal significantly reduced seizure frequency (greater than 50% reduction) over the two years therapy. Beyond "classical" pivotal studies, extension phases reflect the way physicians and patients are managing epilepsy on a day-to-day basis.

"The ability of an anti-epilepsy medication to gain and maintain control of seizures over an extended period of time is an important characteristic," said Tracy Glauser, MD, associate professor of pediatrics and neurology at the Children's Hospital Medical Center in Cincinnati and author of one of the studies. "These data show Trileptal helped reduce seizure frequency over the long term in various epilepsy patient populations."

#### **Study details:**

The first study, presented on 9 December by Dr. Glauser, was an open-label extension phase of a trial that examined the safety and efficacy of Trileptal as adjunctive therapy in children (aged 3-17) who experienced seizures while taking other AEDs. Two hundred and thirty-three children who had been enrolled in a double-blind, placebo-controlled, parallel-group trial entered the study's open-label extension phase. During the two-year extension, 55% of patients experienced a 50% or greater reduction in seizure frequency, 31% of patients experienced a 75% or greater reduction in seizure frequency, and 6% of patients experienced a 100% reduction in seizure frequency. In all, 128 patients completed the two-year open-label extension. The most common adverse events seen in the study were headache (37%), vomiting (36%), somnolence (33%), dizziness (32%), viral infection (27%), fever (24%) and upper respiratory infection (23%).

The second study was presented on 10 December 2002 by Daniela Minecan, MD, clinical assistant professor in the Department of Neurology at the University of Michigan Medical School. Dr. Minecan reported on the two-year open-label extension phase of a study that examined the safety and efficacy of Trileptal as monotherapy in patients (aged 11-66) with partial seizures. In all, 35 of 76 patients completed the additional two years of therapy. Other AEDs were allowed. The maximum allowable dose of Trileptal was 3000 mg/day unless otherwise approved. Overall, 47% of patients experienced a 50% or greater reduction in seizure frequency, 24% experienced a 75% or greater reduction, and 7% experienced a 100% reduction of seizures during this two-year period. Of those on Trileptal as monotherapy, 59% experienced a 50% or greater reduction in seizure frequency, 36% experienced a 75% or greater reduction, and 10% experienced a 100% reduction. Of those receiving Trileptal as adjunctive therapy, 35% experienced a 50% or greater reduction in seizure frequency, 11% experienced a 75% or greater reduction, and 3% experienced a 100% reduction. The most common adverse events were dizziness (46%), headache (32%), fatigue (30%), diplopia (30%), nausea (26%), abnormal vision (21%) and somnolence (21%).

The third study, presented on 10 December 2002 by Steven Schachter, MD, associate professor of neurology at Harvard Medical School, evaluated the two-year open-label extension phase of a trial of Trileptal as monotherapy in partial seizure patients (aged 11-62) who were candidates for surgical treatment of epilepsy. Of the 97 patients who entered the open-label extension phase, 43 completed two years of treatment. The maximum allowable dose was 3000 mg/day unless otherwise approved. During the 10-day double blind treatment phase, 13 of 51 patients treated with Trileptal experienced a 100% reduction in seizures. Five of these patients continued to experience a 100% reduction in seizures during the two-year open-label extension phase. Throughout the two-year period, the most common adverse events were headache (61%), dizziness (58%), diplopia (45%), fatigue (41%), nausea (36%), vomiting (27%), somnolence (24%), viral infection (22%) and abnormal vision (21%).

### **About Trileptal**

Trileptal is an antiepileptic drug with proven efficacy either as a monotherapy or in combination therapy in the treatment of partial seizures (including seizure subtypes of simple, complex, and partial seizures evolving to secondarily generalized seizures) in adults and children with epilepsy.

Trileptal has a favorable safety profile. There is no black box warning and it is not associated with aplastic anaemia, agranulocytosis, hepatotoxicity or pancreatitis. In addition, no monitoring of drug level, liver functions or blood counts is required. As monotherapy in adults, Trileptal is well tolerated, with discontinuation rates comparable to placebo.

Trileptal is not generally associated with weight gain or cosmetic side effects. As monotherapy or adjunctive therapy in adults previously treated with other AEDs, the most common (>5%) adverse events occurring substantially more frequently than in placebo patients were dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, and abnormal gait these were typically mild to moderate in severity. As add-on therapy in pediatric patients, adverse events with Trileptal were similar to adults.

Clinically significant hyponatremia (sodium <125 mmol/L) has been observed in 2.5% of Trileptal-treated patients in controlled clinical trials. Measurement of serum sodium levels should be considered for patients at risk of hyponatremia.

Of patients who have demonstrated hypersensitivity to carbamazepine, 25% to 30% will experience a reaction to Trileptal. Caution should be exercised when prescribing Trileptal for patients with a history of hypersensitivity to carbamazepine. (Please see Warnings section of the complete prescribing information.)

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The foregoing press release contains forward-looking statements that can be identified by forward-looking terminology such as "long term efficacy" or similar expressions, or by express or implied discussions regarding potential revenues from future sales of Trileptal. Such statements involve known and unknown risks, uncertainties and other factors that may cause the actual results to be materially different from any future results, performance, or achievements expressed or implied by such statements. There are no guarantees that the aforementioned clinical trials will result in any additional sales of Trileptal. Any such sales or other results can be affected by, amongst other things, uncertainties relating to product efficacy, regulatory actions or delays or government regulation generally, the ability to obtain or maintain patent or other proprietary intellectual property protection and competition in general, as well as factors discussed in Novartis AG's Form 20-F filed with the Securities and Exchange Commission. Any of these and other factors can cause the actual results to differ materially from the expected or predicted results.

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### MEDIA RELEASE COMMUNIQUE AUX MEDIAS MEDIENMITTEILUNG

#### **Zometa® better than pamidronate in reducing risk of bone complications of advanced breast cancer, according to data presented at major medical meeting**

*Data presented at San Antonio Breast Cancer Symposium; patients have a 20% reduced risk of fractures and other cancer-related bone complications with Zometa*

Basel, 11 December 2002 Zometa® (zoledronic acid) significantly reduced the risk of developing a skeletal-related event (SRE) when compared to pamidronate disodium (Aredia®) in advanced breast cancer patients who were treated for up to twenty-four months, according to data presented today at the San Antonio Breast Cancer Symposium. These SREs include, among others, pathologic fractures, a need for radiation or surgery to bone, spinal cord compression and hypercalcemia. An intravenous bisphosphonate, Zometa is the first therapy of its kind to demonstrate efficacy in treating bone complications across a broad range of tumor types such as breast, prostate, lung and renal cell cancers. Further, Zometa offers patients, nurses and clinicians a convenient 4 mg, 15-minute infusion time.

"Bone metastases and their complications can be severely debilitating for advanced breast cancer patients. These new longer-term data suggest that Zometa offers these patients an effective and convenient treatment that can help reduce their risk of developing these complications," said Robert E. Coleman, MD, lead investigator and Section Head Clinical Oncology, University of Sheffield, United Kingdom.

#### **Clinical Data Results**

In this study, a multiple event analysis demonstrated that breast cancer patients treated with Zometa 4 mg in a 15-minute infusion had a 20% lower risk of developing skeletal complications ( $p=0.025$ ) after two years of treatment, compared with those treated with pamidronate disodium (Aredia®) 90 mg infused over two hours. The multiple event analysis is a rigorous and sensitive assay that measures the occurrence of SREs over the entire course of treatment. Long-term data from this study and others suggest the long-term safety and efficacy of Zometa in the treatment of bone metastases not only in breast cancer but in a broad range of other tumors as well. These data have been submitted and are under review by health authorities in the EU, US and other countries for inclusion in existing labelling.

These data are from three large international clinical trials that evaluated more than 3 000 patients with myeloma, breast cancer, prostate cancer, lung cancer and other solid tumors. This is the largest set of clinical trials ever conducted to evaluate the efficacy and tolerability of a bisphosphonate in treating metastatic bone lesions.

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**About Zometa**

Novartis has received marketing authorization for Zometa in more than 50 countries, including the United States and the European Union Member States, for the prevention of skeletal related events in patients with advanced malignancies involving bone. These malignancies include multiple myeloma, prostate cancer, breast cancer, lung cancer, renal cancer and other solid tumors. Previously, Novartis received marketing clearance for Zometa in the treatment of hypercalcemia of malignancy (HCM), also known as tumor-induced hypercalcemia (TIH), in more than 70 countries throughout the world.

**Contraindications and Adverse Events**

In clinical trials in patients with bone metastases and hypercalcemia of malignancy, 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.

Zometa and other IV bisphosphonates have been associated with reports of renal insufficiency. Patients should have serum creatinine assessed prior to receiving each dose of Zometa. 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.

The foregoing release contains forward-looking statements that can be identified by terminology such as "suggest" or similar expressions, or by discussions regarding potential new indications for Zometa, or regarding potential future sales of Zometa. Such forward-looking statements 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 approved for any additional indications in any market. Neither can there be any guarantee regarding potential future sales of Zometa. In particular, management's ability to ensure satisfaction of the health authorities' further requirements is not guaranteed and management's expectations regarding commercialization of Zometa could be affected by, among other things, additional analysis of Zometa clinical data; new clinical data; unexpected clinical trial results; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; and other risks and factors referred to in the Company's current Form 20-F on file with the Securities and Exchange Commission of the United States. 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.

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Additional information on Novartis Oncology can be found at [www.novartisoncology.com](http://www.novartisoncology.com) or [www.zometa.com](http://www.zometa.com). Additional media information can be found at [www.novartisoncologyvpo.com](http://www.novartisoncologyvpo.com).

**MEDIA RELEASE    COMMUNIQUE AUX MEDIAS    MEDIENMITTEILUNG**

**Novartis Distinguished Scientist Awards and Leading Scientist Awards 2002**

Basel, 11 December 2002 The Novartis Scientist Awards the Distinguished Scientist Award and the Leading Scientist Award for the Pharma Division are conferred today at a formal ceremony. The main speaker at the event will be Professor Mark Fishman, Director of the newly established Novartis Institutes for Biomedical Research. In an address entitled "From Fish to Physician," he will be discussing new options in drug development, from discovery to application.

The Novartis Scientist Awards granted this year for the fifth time are part of the company's global VIVA (Vision, Innovation, Value, Achievement) program, which was established at the end of 1997 to promote creativity and innovativeness in research and development. The awards are designed to recognize exceptional contributions made by scientists working in R&D.

**Distinguished Scientist Award**

The highest internal scientific distinction at corporate level is the Distinguished Scientist Award, which carries a prize of CHF 40 000 as well as the right to use the title "Novartis Distinguished Scientist." This year, the coveted award has been granted to **Dr. André Cordier**, and to **Dr. John R. Fozard**. Dr. Cordier, Global Senior Expert for Toxicology and Pathology in Pharma Development, has made an outstanding contribution in applying the latest findings in the field of genomics and toxicogenomics to investigate the preclinical safety of new active substances. Dr. Fozard, Head research team in the Respiratory Diseases Therapeutic Area, is receiving the award for his outstanding and successful contributions to research into new mechanisms that provide the basis for the development of novel antiasthmatic agents. The work of both of these scientists is highly regarded by the scientific community within Novartis and externally.

**Leading Scientist Award for the Pharma Division**

The highest scientific distinction within the Pharma Division is the Leading Scientist Award, which carries a prize of CHF 25 000 as well as the right to use the title "Novartis Leading Scientist." This year, the award is being granted to the following 12 scientists from Basel and the US: Dr. Reinhard Bergmann, Dr. Bernard Faller, Dr. Roger Fujimoto, Dr. Carlos Garcia-Echeverria, Dr. Wolfgang Jahnke, Dr. Heidi Lane, Dr. Franco Di Padova, and Dr. Stacy Remiszewski (Research); and Dr. Michel Ausborn, Dr. Judit E. Markovits, Dr. Hans-Joerg Martus, and Dr. Mahavir Prashad (Development).

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**Investor Relations Release**

**Study suggests Exelon® effective in patients with mixed dementia**

*In a 26-week study of patients with both Alzheimer's disease and vascular dementia symptoms were significantly improved by the dual cholinesterase inhibitor Exelon®*

Basel, 10 December 2002 Study results presented at a scientific congress in Puerto Rico suggest that the Alzheimer's disease treatment Exelon® (rivastigmine) is effective and well tolerated in patients suffering from Alzheimer's disease with vascular features, also known as "mixed" dementia. The open-label study<sup>1</sup> demonstrated that after 26 weeks of treatment with Exelon patients had significant benefit in cognition (thinking, memory, speech) and behavioral symptoms. They were also better able to carry out activities of daily living, such as bathing and dressing.

"This is the first time anyone has looked at the efficacy of Exelon in mixed dementia," said Professor Michael Roesler, lead author of the study and a psychiatrist at the Homburg/Saar University Hospital in Germany. "We are very encouraged by the results which indicate that Exelon is an effective treatment for patients with mild to moderate mixed dementia."

Alzheimer's disease (AD) is the most common form of dementia, accounting for about 55% of cases, followed by vascular dementia (VaD). However, many patients with AD also have some VaD pathology and are therefore classified as having "mixed" dementia. Both conditions are associated with deficits of the neurotransmitter acetylcholine.

In addition to its effectiveness in mixed dementia, Exelon also appears to work in other vascular-related dementias. Evidence to support this comes from two recently published studies. The first, conducted by Dr Rita Moretti<sup>2</sup> at the University of Trieste in Italy, showed that long term therapy with Exelon was effective in subcortical vascular dementia. In another investigation, led by Dr Timo Erkinjuntti<sup>3</sup> at Helsinki University Central Hospital, Finland, Exelon effectively treated the symptoms of AD with hypertension.

Exelon works by inhibiting the two enzymes responsible for breaking down acetylcholine in the brain: acetylcholinesterase and butyrylcholinesterase. By blocking the action of both enzymes, Exelon maintains brain function for longer by increasing the amount of acetylcholine available for nerve signal transmission.

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**Study and Results**

A total of 80 patients at treatment centers across Germany took part in the study. The mean age was 74.4 years and patients were equally divided between "mild" and "moderate" dementia. After 26 weeks of Exelon treatment, cognitive function improved significantly, with an increase in ADAS-cog<sup>4</sup> scores of over 3.5 points (P<0.001). On a global rating of change, at least three-quarters of patients showed improvement.

Behavioral symptoms of dementia were significantly reduced compared to baseline scores in this study, with mean NeuroPsychiatric Inventory (NPI) scores 0.9 points lower (P=0.0435). This was reflected in reduced caregiver distress scores. Patients' ability to carry out daily activities was also improved with an increase of 0.8 points on the CIBIC-plus<sup>5</sup> "everyday life function" subscale score (P=0.0001).

Exelon was well tolerated by study participants with the most common adverse events being gastrointestinal. Exelon was not associated with any cardiac events. Sixty-one patients completed the study.

**About Alzheimer's disease**

Alzheimer's disease is a neurodegenerative disease involving deterioration of the brain. It is the fourth leading cause of death behind cardiovascular disease, cancer, and stroke and affects up to four million adults in the United States and more than 10 million worldwide. It has an annual US price tag of approximately \$100 billion in direct (healthcare and related) and indirect (income) costs.

This press release contains forward looking statements which can be identified by the use of forward-looking terminology such as "suggest", "show", "indicate", "also appear", "evidence to support" or similar expressions, or by expressed or implied discussions regarding potential additional indications for Exelon, or potential additional revenue to Novartis from Exelon sales. Such forward looking statements

involve known and unknown risks, uncertainties and other factors that may cause actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. There are no guarantees that the aforementioned clinical trials will result in any additional indications for Exelon in any market, or in any additional revenue to Novartis from Exelon sales. Any such results can be affected by, amongst other things, uncertainties relating to product development, including uncertainties regarding the outcome of clinical trials, regulatory actions or delays or government regulation generally, the ability to obtain or maintain patent or other proprietary intellectual property protection and competition in general, as well as factors discussed in Novartis AG's Form 20-F filed with the Securities and Exchange Commission. Any of these and other factors can cause the actual results to differ materially from the expected or predicted results.

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1. M Roesler, HE Klein, M Ackenheil. An open study evaluating the efficacy and safety of rivastigmine in patients with mixed dementia. Presentation at ACNP, Puerto Rico, December 2002.
  2. R Moretti, P Torre, RM Antonello, G Cazzato, A Bava. Rivastigmine in subcortical vascular dementia: An open 22-month study. *J Neurol Sci* 2002; 203 204: 141 146.
  3. T Erkinjuntti, I Skoog, R Lane, C Andrews. Rivastigmine in patients with Alzheimer's disease and concurrent hypertension. *Int J Clin Pract* 2002; 56: 791 796.

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4. Alzheimer's Disease Assessment Scale-cognition.
  5. Clinicians' Interview Based Impression of Change.

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**MEDIA RELEASE COMMUNIQUE AUX MEDIAS MEDIENMITTEILUNG**

**Novartis Launches Z-FAST: A Study Evaluating Femara® and Zometa® in Postmenopausal Women with Early Breast Cancer**

*Study of 500 women combines Femara, a leading aromatase inhibitor, with Zometa, the most widely used IV bisphosphonate. Z-FAST will evaluate adjuvant cancer treatment-related bone loss in postmenopausal women with early breast cancer*

Basel, 10 December, 2002 Novartis announced today that it is combining two widely used drugs in a trial to evaluate bone loss associated with cancer treatment in postmenopausal women with early breast cancer. The Novartis drugs being paired are Femara® (letrozole tablets), a leading aromatase inhibitor in advanced breast cancer, and Zometa® (zoledronic acid), the most widely used IV bisphosphonate in treating bone complications of advanced cancer. The study, Z-FAST (Zometa/Femara Adjuvant Synergy Trial) is a multicenter trial designed to help address two important and unanswered clinical questions facing the breast cancer community: 1) Does treating early breast cancer with an aromatase

inhibitor cause bone loss? 2) Can potential bone loss be reduced by including a potent IV bisphosphonate in the treatment paradigm? The study will provide valuable data for the patient population likely to benefit from this information postmenopausal women receiving aromatase inhibitor therapy for early breast cancer in the adjuvant setting.

In postmenopausal women, aromatase inhibitors suppress the production of estrogen, a hormone that can promote growth of receptor positive breast cancer. Although the reduction of estrogen may be beneficial in the treatment of breast cancer, long-term use of aromatase inhibitors may also cause bone loss. Aromatase inhibitors such as Femara are becoming more widely studied in early breast cancer.

In the early breast cancer setting, aromatase inhibitors will be used for extended periods of time, making prevention of bone loss an important consideration. The study will evaluate the benefit of adding a potent IV bisphosphonate, Zometa, to an aromatase inhibitor, Femara, in postmenopausal women with early breast cancer in order to offer patients the potential to combine the efficacy of Femara with the bone protective effects of Zometa.

"There is a pressing clinical need to address the bone loss concerns of postmenopausal women with early breast cancer," said Adam Brufsky, M.D, Ph.D., Principal Investigator, Magee/UPCI Breast Program, University of Pittsburgh Cancer Institute. Richard Theriault, D.O., M.B.A., Co-Principal Investigator, Department of Breast Medical Oncology MD Anderson Cancer Center, added, "If proven successful, the combination of Femara and Zometa could change the treatment paradigm for many patients by simultaneously providing them with effective breast cancer treatment and bone loss protection in the adjuvant setting."

### **Study Design**

This open-label, randomized, multicenter trial will enroll approximately 500 postmenopausal women with stage I, II, IIIa, ER and/or PR+ breast cancer who have undergone complete tumor resection, and no clinical or radiological evidence of recurrent or metastatic disease, at up to 120 centers in the United States and Canada.

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Patients will remain in the study and be treated for a maximum of five years, or until disease progression, with Femara as their adjuvant therapy beginning Day one. Patients will be randomized to one of two Zometa treatment arms, receiving either an upfront 4 mg, 15-minute infusion of Zometa every 6 months beginning on day one or a delayed start 4 mg, 15-minute infusion of Zometa every 6 months. The initiation of delayed start Zometa will be determined by a post-baseline bone mineral density below 2.0 SD.

### **Additional Adjuvant Studies**

Enrollment for a similar study, ZO-FAST (Zometa/Femara Adjuvant Synergy Trial) will begin in approximately 30 countries outside the US. in January 2003. Nine hundred patients are expected to participate. In addition to evaluating postmenopausal women, ZO-FAST will be open to newly postmenopausal women in whom menopause has been artificially induced by medically intervention, i.e. estrogen suppressive therapy or chemotherapy.

Novartis has two ongoing adjuvant trials (MA-17 and BIG 1-98) with Femara, involving almost 13,000 postmenopausal women. Collectively, these trials comprise one of the largest evaluations of an aromatase inhibitor in the adjuvant setting.

MA-17 is being conducted by the National Cancer Institute of Canada Clinical Trials Group, and is designed to determine the disease-free and overall survival of postmenopausal women (ER+ and/or ER receptor unknown) taking Femara after at least five years of tamoxifen therapy compared to women taking placebo after at least five years of therapy. MA-17 reached its enrollment milestone of 4,800 patients earlier this year (August 30, 2002).

A second Phase III adjuvant study with Femara is being conducted by the Breast International Group (BIG 1-98) in collaboration with Novartis. This study has four treatment arms comparing: five years of Femara, five years of tamoxifen, two years of Femara followed by three years of tamoxifen, and two years of tamoxifen followed by three years of Femara. The BIG 1-98 trial has enrolled 7,105 patients to date with a targeted enrollment of 7,952. Results for both studies are expected to be available in 2004.

### **About Femara and Zometa**

Femara, an aromatase inhibitor, is an oral once-a-day first-line treatment for postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer. It is also approved for the treatment of advanced breast cancer in



postmenopausal women with disease progression following antiestrogen therapy, and as neo-adjuvant (pre-operative) therapy. Femara is currently available in more than 75 countries worldwide. Not all indications are approved in every country.

Novartis has received marketing authorization for Zometa in more than 50 countries, including the United States and the European Union Member States, for the prevention of skeletal related events in patients with advanced malignancies involving bone. These malignancies include multiple myeloma, prostate cancer, breast cancer, lung cancer, renal cancer and other solid tumors. Previously, Novartis received marketing clearance for Zometa in the treatment of hypercalcaemia of malignancy (HCM), also known as tumour-induced hypercalcaemia (TIH), in more than 70 countries throughout the world.

#### **Femara Contraindications and Adverse Effects**

Femara is contraindicated in patients with known hypersensitivity to Femara or any of its excipients. Femara is generally well tolerated and adverse reactions rates in the first-line study in which Femara was compared to tamoxifen were similar with those seen in second-line studies. The most commonly reported adverse events for Femara vs. tamoxifen were bone pain, hot flushes, back pain, nausea, dyspnea or labored breathing, arthralgia, fatigue, coughing, constipation, chest pain and headache. Femara may cause fetal harm when administered to pregnant women. There is no clinical experience to date on the use of Femara in combination with other anticancer agents.

#### **Zometa Contraindications and Adverse Effects**

In clinical trials in patients with bone metastases and hypercalcemia of malignancy, 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.

Zometa and other IV bisphosphonates have been associated with reports of renal insufficiency. Patients should have serum creatinine assessed prior to receiving each dose of Zometa. 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.

The foregoing release contains forward-looking statements that can be identified by forward-looking terminology such as "will," "to evaluate," "designed to," "could change," or similar expressions, or by express or implied discussions regarding discussions regarding potential new indications for Femara or Zometa, or regarding potential future sales of Femara or Zometa. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results with these drugs to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that the clinical trials described above will result in Femara or Zometa being approved for any additional indications in any market. Neither can there be any guarantee regarding potential future sales of Femara or Zometa. In particular, management's ability to ensure satisfaction of the health authorities' further requirements is not guaranteed and management's expectations regarding commercialization of Femara and Zometa could be affected by, among other things, unexpected clinical trial results, including the results of the clinical trials described above; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; and other risks and factors referred to in the Company's current Form 20-F on file with the Securities and Exchange Commission of the United States. 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.

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Additional information on Novartis Oncology, Zometa and Femara can be found at [www.novartisoncology.com](http://www.novartisoncology.com), [www.zometa.com](http://www.zometa.com) and [www.femara.com](http://www.femara.com). Additional media information can be found at [www.novartisoncologyvpo.com](http://www.novartisoncologyvpo.com).

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**Investor Relations Release**

**New longer-term data show Glivec nine times more likely than interferon combination to achieve chronic myeloid leukemia key treatment goal**

*18-month data highlighted at annual meeting of the American Society of Hematology (ASH) show Glivec significantly more likely to eliminate Philadelphia chromosome in CML patients*

*Highest Glivec response rates achieved with early, first-line use*

Basel, 9 December 2002 Updated data from the first head-to-head study of the Novartis drug Glivec® (imatinib) demonstrate that chronic myeloid leukemia (CML) patients are nine times more likely to achieve a complete cytogenetic response taking Glivec (74%) than those treated with a combination of interferon-alpha and cytosine arabinoside (IFN/Ara-C) [8%], a traditional treatment for CML. A complete cytogenetic response is the elimination of Philadelphia chromosome-positive cells (Ph+), the genetic abnormality that characterizes most cases of CML, and is a major goal of treatment. Additionally, significantly fewer patients in the Glivec arm have progressed to advanced stages of CML compared with those in the IFN/Ara-C arm. The new 18-month data, from the International Randomized Study of Interferon vs. STI571 (IRIS), were presented at the plenary session of the 2002 meeting of the American Society of Hematology (ASH) in Philadelphia, Pennsylvania.

"The 18-month IRIS data demonstrate that Glivec significantly delays progression to the more advanced stages of the disease," said David Parkinson, MD, Vice President of Clinical Research, Novartis Oncology.

**Clinical Data**

The new data were updated from 12-month IRIS results, which had been presented earlier this year at the annual meeting of the American Society of Clinical Oncology (ASCO).

At the 18-month follow-up, 74% of newly diagnosed patients treated with Glivec at 400 mg daily achieved a complete cytogenetic response (no detection of cells containing the Ph+ chromosome), compared with 8% of those treated with the combination therapy of IFN/Ara-C (P<0.001)\*\*. A major cytogenetic response (defined as the detection of less than 35% Ph+ cells remaining) was achieved by 85% of patients taking Glivec compared with 22% of patients treated with IFN/Ara-C (P<0.001).

Patients taking Glivec had an improved overall progression-free survival compared with those taking IFN/Ara-C (at 18 months: 92.3% vs. 73.6%, respectively;  $P < 0.001$ ). Progression was defined as progression to accelerated phase or blast crisis, rapid increase in white blood cell count, loss of either complete hematologic response or major cytogenetic response, or death during treatment. In particular, the estimated probability of being free of progression to accelerated phase or blast crisis at 18 months was also significantly higher for those patients taking Glivec (96.7%) compared with those patients taking IFN/Ara-C (control arm) (91.5%), regardless of crossover ( $P < 0.001$ ).

In the Glivec arm, only 2% and 0.7% of patients withdrew from the study or crossed over to the control arm for tolerability reasons, respectively. In contrast, 6% and 25% of patients, respectively, in the IFN/Ara-C arm withdrew from the study or crossed over to the Glivec arm for tolerability reasons.

#### **Additional presentations at ASH**

During the ASH meeting, more than 170 abstracts and presentations featured data on Glivec, including studies on molecular response, cost effectiveness, quality of life and survival data.

*Molecular Response* One of these abstracts<sup>1</sup> will be the focus of an oral presentation by Timothy Hughes, MD, of the Division of Haematology at the Institute of Medical and Veterinary Science, Adelaide, Australia on 9 December at 10:30 a.m. It will provide data from an analysis of those IRIS participants who had achieved a complete cytogenetic response at 12 months and had PCR samples available. In that group, those taking Glivec had a greater chance of achieving minimal residual disease (absence or near absence of Ph+ cells) than those taking IFN/Ara-C, as measured by PCR.

*Cost Analysis* Another presentation<sup>2</sup> of the IRIS data from Shelby Reed, PhD, of the Center for Clinical and Genetic Economics, Duke Clinical Research Institute, Durham, North Carolina, USA, compared costs and resource utilization for patients taking IFN/Ara-C with those taking Glivec. Researchers found that patients randomized to IFN/Ara-C were hospitalized more than twice as often (0.40 days per month) as patients randomized to Glivec (0.16 days per month;  $P < 0.05$ ).

Total monthly costs (inpatient, outpatient and costs of medications) for patients initially treated with Glivec were estimated at USD \$2,512 per month compared to \$2,436 per month for patients initially treated with IFN/Ara-C, resulting in a cost difference of only \$76 per month. As such, the researchers conclude that reserving the use of Glivec for second-line treatment is not associated with a cost advantage, but saving Glivec for second line treatment does result in poorer outcome.

*Quality of Life* A study<sup>3</sup> from Elizabeth Hahn, MA, of the Center on Outcomes, Research and Education, Evanston Northwestern Healthcare, Evanston, Illinois, USA, showed that patients who crossed over to the Glivec arm of the study reported higher quality of life, than those who remained on IFN/Ara-C. The data will be presented on 9 December at 10:45 a.m.

*Survival Data* Another study,<sup>4</sup> by Richard Silver, MD, of the New York-Weill Cornell Department of Medicine, New York City, New York, USA, will feature time-to-progression (TTP) data and survival rates for accelerated phase patients taking Glivec. Data from this study will be presented on 9 December at 3:15 p.m.

#### **Glivec**

In most countries where Glivec is approved, it is indicated for the treatment of patients with Philadelphia chromosome-positive CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. The effectiveness of Glivec is based on overall hematologic and cytogenetic response rates.

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Novartis has also submitted global marketing applications with health authorities seeking marketing authorization for Glivec for the first-line treatment of patients with newly diagnosed Ph+ CML. On 20 September 2002, Glivec received a positive opinion from the Committee for Proprietary Medicinal Products (CPMP) of the EU for this indication. In the U.S., the application was granted priority review status for this indication, which means that the Food and Drug Administration will act on this application no later than six months after the filing date, or by 28 December 2002. Recently, Switzerland became the first country in Europe to approve Glivec for first-line use in adult and pediatric patients with Ph+ CML in chronic phase, accelerated phase and blast crisis.

Glivec received a second EU approval on 31 May 2002, for the treatment of patients with Kit (CD 117)-positive unresectable (inoperable) and/or metastatic malignant gastrointestinal stromal tumors (GISTs). Glivec was designated orphan drug status for GIST in February 2002. Glivec received FDA approval for the treatment of patients with Kit (CD 117) positive unresectable (inoperable) and/or metastatic malignant

gastrointestinal stromal tumors (GISTs).

### Contraindications and Adverse Events

In the first-line study (IRIS), the safety profile with Glivec at the 12-month checkpoint was similar to that of previous Phase II studies in other CML patients. The majority of patients treated with Glivec experienced adverse events at some time. Most events were of mild to moderate grade and treatment was discontinued for adverse events only in 2% of patients in chronic phase, 3% in accelerated phase and 5% in blast crisis. The most common side effects included nausea, fluid retention, vomiting, diarrhea, hemorrhage, muscle cramps, skin rash, fatigue, headache, dyspepsia and dyspnea, as well as neutropenia and thrombocytopenia.

The foregoing release contains forward-looking statements that can be identified by terminology such as "will," or similar expressions, or by discussions regarding potential new indications for Glivec, or regarding the long-term impact of a patient's use of Glivec. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results with Glivec to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that Glivec will be approved for any additional indications in any market. Neither can there be any guarantee regarding the long-term impact of a patients' use of Glivec. In particular, management's ability to ensure satisfaction of the health authorities' further requirements is not guaranteed and management's expectations regarding commercialization of Glivec could be affected by, among other things, additional analysis of Glivec clinical data; new clinical data; unexpected clinical trial results; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; and other risks and factors referred to in the Company's current Form 20-F on file with the U.S. 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.

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*Additional information on Novartis Oncology and Glivec can be found at [www.novartisoncology.com](http://www.novartisoncology.com) or [www.glivec.com](http://www.glivec.com). Additional media information can be found at [www.novartisoncologyvpo.com](http://www.novartisoncologyvpo.com).*

1. "Molecular Responses to Imatinib (STI571) or Interferon + Ara-C as Initial Therapy for CML; Results in the IRIS Study".
2. Within-Trial Resource Utilization and Costs of Patients Randomized to Treatment with Imatinib (STI571) Versus Interferon-Alpha (IFN- $\alpha$ ) Combined with Cytarabine (Ara-C) in Newly Diagnosed Patients with Chronic Myeloid Leukemia in Chronic Phase".
3. "Quality of Life of Patients with Chronic Phase Chronic Myeloid Leukemia in the IRIS Study of Interferon-Alpha Plus Ara-C vs Imatinib (STI571, Glivec, Gleevec)".
4. "Imatinib (STI571, Glivec) Achieves Prolonged Survival in Patients with Accelerated Phase Ph+ Chronic Myeloid Leukemia (CML-AP): Up to 36 Months Follow-Up of a Phase II Study".

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### Investor Relations Release

#### **Investigational oral drug from Novartis demonstrated favorable results in patients with excess iron from transfusion-dependent anemias; new data featured at major US medical meeting**

*Phase II data suggest new oral tablet for serious chronic iron overload in transfusion-dependent anemias provides benefits comparable to the most widely-prescribed iron chelator (Desferal®); without lengthy 8-12 hour infusion. Phase II and III studies in thalassemia and sickle cell disease to start early 2003*

Basel, 9 December 2002 New data featured at a major medical meeting suggest that a once-daily oral dose of a Novartis iron-chelating investigational drug (ICL670) may be as effective as the most widely prescribed treatment, Desferal® (deferoxamine mesylate for injection USP), which is usually administered daily via a continuous infusion over eight to 12 hours. The new compound is being evaluated in patients with chronic iron overload, a potentially life-threatening condition resulting from repeated blood transfusions in certain anemias. The data, from an ongoing Phase II study in 71 patients with thalassemia, were presented at the annual meeting of the American Society of Hematology (ASH) in Philadelphia. In the trial, the oral iron-chelator ICL670 demonstrated benefits comparable to the infused therapy, Desferal (also from Novartis), but via a convenient oral administration. Thalassemia is a congenital disorder resulting in production of abnormal hemoglobin; treatment requires frequent blood transfusions that subsequently can lead to too much iron in organs of the body.

"While Desferal has improved patient outcomes, its injectable route of administration creates a significant compliance problem. Although efficacy is the most critical consideration, we also have to take into account the convenience or inconvenience of administering treatment," said lead investigator, Antonio Piga, MD, Turin University, Italy. "If the trial results with ICL670 continue to be favorable and the product is approved by the health authorities, ICL670 should overcome the compliance problems these patients have faced for decades."

#### **Study Details**

The Phase II data featured at ASH were from an open-label, randomized, multicenter study in patients with iron overload resulting from transfusional treatment of  $\beta$ -thalassemia. The 12-month study was designed to compare the overall safety, tolerability and efficacy of ICL670 (orally, either 10 or 20 mg/kg/day) relative to Desferal (40 mg/kg/day, subcutaneously 5 days/week) by measuring decreases in liver iron concentrations (LIC). The LIC reflect the overall body iron burden and were measured every three months by SQUID (Superconducting QUantum Interference Device), a sophisticated and non-invasive technique that provides results quantitatively equivalent to liver biopsy.

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At the nine-month checkpoint reported, LIC in 63 patients taking 10 or 20 mg/kg of ICL670 decreased by 5.61% and 26.3% on average, respectively, compared with 13.9% of 20 patients in the Desferal group. The average liver iron decrease was greater in patients treated with 20 mg/kg/day of ICL670 (-2.2 mgFe/g liver) than those treated with Desferal (-1.2 mgFe/g liver) or 10 mg/kg/day of ICL670 (-0.6 mgFe/g liver).

#### **About Iron Overload**

Iron overload can result from frequent blood transfusions required to treat certain types of anemia caused by genetic defects or other factors. It also can result from genetic defects that cause excessive intestinal absorption of iron from food. Two types of anemia in particular, thalassemia and sickle cell anemia, both congenital disorders in which there is a defect in the production of hemoglobin (the oxygen-carrying substance found in red blood cells) may require frequent transfusions, which subsequently can lead to iron overload. Undiagnosed and untreated, iron overload can lead to debilitating and life-threatening consequences over time. Although effective, the iron chelation treatment (Desferal) for patients with iron overload requires lengthy and frequent subcutaneous infusions of between eight and 12 hours daily. As a result, treatment compliance has been a problem.

#### **ICL670 Development**

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A highly potent oral chelator, ICL670 is being developed by Novartis. The drug has been found to selectively mobilize and promote the elimination of tissue iron. It was granted orphan drug status in March 2002 in the European Union and in November 2002 in the US. In the EU, the term "orphan drug" refers to a product that treats a serious and debilitating disease that affects fewer than five people per 10 000 population.

Global Phase III trials intended to study the drug in patients with transfusion-dependent anemias will be initiated in January 2003 in several countries, including the US. These studies predominantly will include patients with thalassemia; however, the studies also will enroll patients with other transfusion-dependent anemias, including sickle cell disease.

### Contraindications and Adverse Events

In studies to date, overall the drug has been well tolerated with some nausea, vomiting and skin rashes seen at higher doses, however, no unmanageable toxicities have been observed. Safety will be monitored carefully during the clinical trials.

### About Desferal

In the US, Desferal is indicated for removal of excess iron after multiple transfusions. A chelating agent, Desferal binds to free iron molecules in plasma (thereby competing with the body's own transport proteins) and enables the iron to be excreted in urine. Desferal is also indicated as an adjunct to therapy or part of the treatment regimen for acute, accidental or intentional iron overdose. Desferal is contraindicated in patients with severe renal disease or anuria, since the drug and the iron chelate are excreted primarily by the kidney. In addition, ocular and auditory disturbances have been reported when Desferal was administered over prolonged periods of time, at high doses or in patients with low ferritin levels.

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The foregoing release contains forward-looking statements that can be identified by terminology such as "suggest," "to start," "may be," "will be initiated," or similar expressions, or by discussions regarding the potential approval of ICL670. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results with ICL670 to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that ICL670 will be approved for sale in any market. In particular, management's expectations regarding commercialization of ICL670 could be affected by, among other things, additional analysis of ICL670 clinical data; new clinical data; unexpected clinical trial results; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; and other risks and factors referred to in the Company'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.

### About Novartis

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Additional information on Novartis Oncology and ICL670 can be found at [www.novartisoncology.com](http://www.novartisoncology.com). Additional media information can be found at [www.novartisoncologyvpo.com](http://www.novartisoncologyvpo.com).

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### Investor Relations Release

#### **Glivec® (imatinib) approved in Switzerland for first-line treatment of adults and children with chronic myeloid leukemia (CML), allowing broader, earlier use**

Basel, 4 December 2002 Novartis announced today that the Swiss Agency for Therapeutic Products (Swissmedic) has approved two new indications for Glivec®\* (imatinib), broadening its use to include first-line treatment of patients with newly diagnosed chronic myeloid leukemia (CML) as well as for pediatric patients in all phases of the disease. Previously, Glivec had been indicated only for the treatment of adult CML in the blast crisis, accelerated phase or in chronic phase after failure of interferon-alpha therapy.

The marketing application for the first-line indication was based on 12-month data from the International Randomized Study of Interferon plus Ara-C vs Glivec (IRIS), a large head-to-head study comparing Glivec with a combination of the biologic agent interferon-alpha, and the chemotherapy drug cytosine arabinoside (IFN/Ara-C), a traditional treatment for CML. In this study, 83% of patients treated with Glivec given orally at 400 mg per day achieved a major cytogenetic response at 12 months, compared with 20% for the combination of IFN/Ara-C.

The 12-month data from IRIS were presented at the 2002 Annual Meeting of the American Society of Clinical Oncology (ASCO, Orlando, May 18-21, B. Druker et al.). Updated 18-month data from the same study show continued superior results with Glivec. These data will be presented in the plenary session of the 2002 annual meeting of the American Society of Hematology (ASH, Philadelphia, December 8, R. Larsen et al.).

#### **Progression significantly delayed**

The IRIS study showed that Glivec significantly delayed the time to progression to the more advanced stages of CML, compared with IFN/Ara-C. Progression was defined as progression to accelerated phase or blast crisis, rapid increase in white blood cell count, loss of either complete hematologic response or major cytogenetic response, or death during treatment. The data also show that newly diagnosed CML patients treated with Glivec had a significantly better quality of life than those treated with the combination therapy.

Swissmedic also approved Glivec for the treatment of pediatric patients in all phases of CML. The efficacy (cytogenetic response) and safety profile of Glivec in children at least three years old have been shown to be similar to those seen in adults.

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#### **Glivec**

In most countries in which it is approved, Glivec is indicated for the treatment of patients with Ph+ CML in the blast crisis, accelerated phase or in chronic phase after failure of interferon-alpha therapy. In February 2002, just nine months following the initial CML approval, Glivec received FDA approval for the treatment of patients with Kit (CD 117) positive unresectable (inoperable) and/or metastatic malignant gastrointestinal stromal tumors (GISTs). The GIST indication also was approved on 24 May 2002 in the EU.

#### **Contraindications and Adverse Events**

The most common side effects of treatment with Glivec include nausea, fluid retention, vomiting, diarrhoea, muscle cramps, skin rash, fatigue, headache, dyspepsia, abdominal pain, myalgia, as well as neutropaenia and thrombocytopaenia. Glivec is often associated with oedema and occasionally serious fluid retention, GI irritation and severe hepatotoxicity.

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Glivec is contraindicated in-patients with known hypersensitivity to imatinib or any of its excipients. Women of childbearing potential must be advised to use effective contraception during treatment of Glivec.

In the first-line study (IRIS), the safety profile with Glivec at the 12-month follow-up was similar to that of previous Phase II studies in other CML patients. The majority of patients treated with Glivec experienced adverse events at some time. Most events were of mild to moderate grade and treatment was discontinued for adverse events only in 2% of patients in chronic phase, 3% in accelerated phase and 5% in blast crisis. The most common side effects included nausea, fluid retention, vomiting, diarrhea, hemorrhage, muscle cramps, skin rash, fatigue, headache, dyspepsia and dyspnea, as well as neutropenia and thrombocytopenia.

The foregoing release contains forward-looking statements that can be identified by terminology such as "allowing broader, earlier use," or similar expressions, or by discussions regarding potential new indications for Glivec, or regarding the long-term impact of a patient's use of Glivec. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results with Glivec to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that Glivec will be approved for any additional indications in any market. Neither can there be any guarantee regarding the long-term impact of a patient's use of Glivec. In particular, management's ability to ensure satisfaction of the health authorities' further requirements is not guaranteed and management's expectations regarding commercialization of Glivec could be affected by, among other things, additional analysis of Glivec clinical data; new clinical data; unexpected clinical trial results; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; and other risks and factors referred to in the Company's current Form 20-F on file with the U.S. 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.

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### MEDIA RELEASE COMMUNIQUE AUX MEDIAS MEDIENMITTEILUNG

#### Novartis completes Health & Functional Food divestment to Associated British Foods

Basel, 2 December 2002 Novartis announced today that it has completed the divestment of its Food & Beverage (F&B) business to Associated British Foods plc (ABF) for a total of 272.5 million Euros (approximately CHF 400 million). The transaction, which includes the Ovaltine/Ovomaltine brand, was announced in October and is part of the Group's strategy of focusing on healthcare and its core pharmaceuticals business. The F&B business generated overall sales of CHF 366 million (244 million Euros) in 2001.

Associated British Foods is an international food, ingredients and retail group with annual sales of GBP 4.4 billion and 34 000 employees. The Group is one of Europe's largest food companies with a wide range of successful brands and products in the food sector, and an increasingly strong presence in advanced research and technology, where it is turning natural products into innovative ingredients for the food, personal care and pharmaceutical industries. A significant supplier of branded and non-branded grocery products and a leading textile retailer, ABF has significant businesses in Europe, Australia, New Zealand, China and the USA.

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information please consult <http://www.novartis.com>.

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**MEDIA RELEASE COMMUNIQUE AUX MEDIAS MEDIENMITTEILUNG**

**Novartis initiates largest global clinical trial of Zelmac® in IBS**

*ZENSAA Study Seeks to Enroll 2,500 Women Worldwide*

Basel, 2 December 2002 Clinical researchers in primary care and specialty gastroenterology practices worldwide have just started recruiting patients for the largest clinical trial to be conducted in Irritable Bowel Syndrome (IBS). The objective of the ZENSAA study is to assess the efficacy and safety of repeated treatment with the novel Novartis drug Zelmac®\* (tegaserod), in female patients with IBS with constipation, who experience a positive response during initial treatment but whose symptoms recur after treatment is stopped.

The ZENSAA study seeks to enroll 2,500 women aged 18-65 years who suffer from IBS with constipation. The study will be conducted at 262 centers in 24 countries, including the United States, United Kingdom, Canada, Mexico, Germany, France, Italy, Spain, South Africa and New Zealand. Zelmac is currently available in more than 30 countries including Australia, Switzerland, Canada, the United States and Brazil.

IBS is a chronic, episodic condition characterized by abdominal pain and discomfort, bloating, and altered bowel function (constipation and/or diarrhea). The prevalence of IBS differs by country, however recent studies suggest that the disorder affects approximately 10-20% of the Western population up to 1 in 5 adults.

"IBS affects millions of women worldwide, and this study will examine the ability of Zelmac to relieve the multiple symptoms of IBS with constipation in a situation that closely duplicates actual clinical practice," said Joerg Reinhardt, Head of Development, Novartis Pharma AG. "The symptoms of IBS come and go, and vary in intensity throughout the course of the disease, having a very serious impact on patients' lifestyles."

**About the ZENSAA Study**

This study is a prospective, randomized, double blind, parallel group, multicenter trial comparing Zelmac at 6 mg twice daily (b.i.d.) to placebo, in female patients with IBS with constipation. Primary efficacy variables are overall relief of IBS symptoms and overall relief of abdominal pain/discomfort. Efficacy will be measured by patient responses to several assessment questionnaires, recorded in electronic diaries. In addition, patients will be asked to record their abdominal discomfort or pain, bloating, constipation and bowel habits on a daily and weekly basis in the electronic diaries.

Secondary efficacy variables include the individual gastrointestinal (GI) symptoms of IBS such as pain/discomfort and bloating (daily) and constipation (weekly) and the time of onset of GI symptom relief. The study is designed to mirror clinical practice as closely as possible in the clinical trial setting.

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In addition to the efficacy and safety assessments, the study will also evaluate the impact of Zelmac vs. placebo on patient quality of life. Patients will be asked to complete the Hospital Anxiety and Depression Scale (HADS), an Overall Satisfaction with Treatment questionnaire,

and a Work-Productivity Activity Impairment for IBS questionnaire. The data from each, except HADS, will be used for secondary efficacy evaluation. Data from the HADS evaluation will be used for characterization of the study populations in each treatment period.

The study was designed in close collaboration with the Committee for Proprietary Medicinal Products of the European Health Authorities, to ensure the protocol meets the highest scientific standards and fulfills their requirements. In addition, the study will provide important insight into the time-course of IBS, and a more thorough understanding of the disease in general.

#### **About Irritable Bowel Syndrome**

Until recently, the cause of IBS has been poorly understood and under-estimated. However, in recent years, new research has yielded a better understanding of IBS and its causes. People who have abdominal pain and discomfort, bloating and constipation associated with IBS may have altered sensitivity and altered motility of their lower GI tract. This may be due to the way their lower GI tract reacts to changes in serotonin (5HT), a naturally occurring chemical in their body that regulates motility and perception of pain and discomfort in the intestinal system.

#### **About Zelmac**

Zelmac is the first in a new class of medicines, known as serotonin-4 receptor agonists (5HT<sub>4</sub> agonists) developed especially for the treatment of the multiple symptoms associated with IBS with constipation. By activating 5HT<sub>4</sub> receptors in the gastrointestinal tract, Zelmac normalizes impaired motility and reduces sensitivity of the intestinal tract. In clinical studies, significantly more patients experienced a general relief of symptoms when treated with Zelmac, such as a decrease in abdominal pain, bloating and constipation. In most patients, the onset of relief occurred within just one week. The medicine was well tolerated and showed a profile of side effects similar to that of placebo. Zelmac was discovered and developed by Novartis and is known as Zelnorm in the United States and Canada.

The foregoing press release contains certain forward-looking statements related to the business of Novartis, which can be identified by the use of forward-looking terminology such as "to be conducted," "to assess," "seeks to enroll," "will," or similar expressions, or by express or implied discussions regarding potential new indications for Zelmac, or the potential for additional revenue from Zelmac sales. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that the ZENSAA study will lead to any new indications for Zelmac, or to any additional revenue from Zelmac sales. Management's expectation regarding the commercial potential of Zelmac in any market could be affected by, amongst other things, uncertainties relating to the outcome of the ZENSAA study and to product development generally, regulatory actions or delays or government regulation generally, the ability to obtain or maintain patent or other proprietary intellectual property protection and competition in general, as well as factors discussed in the Company's Form 20-F filed with the 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 described herein as anticipated, believed, estimated or expected.

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#### **SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

NOVARTIS AG

Date: December 31, 2002

By:

/s/ MALCOLM B. CHEETHAM

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Malcolm B. Cheetham

*Head Group Financial Reporting and Accounting*

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