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## **Novartis remains committed to making Zelnorm® available for women with irritable bowel syndrome with constipation in Europe**

- *Novartis to appeal CHMP opinion against EU approval of Zelnorm*
- *New ZENSAA trial results show Zelnorm provides important relief for multiple symptoms of irritable bowel syndrome with constipation (IBS-C)*
- *Extensive clinical data involving over 14,000 patients and approvals in 56 countries, including US, clearly demonstrate clinical benefits to patients*

**Basel, December 15, 2005** – Novartis will appeal an opinion from a European Medicines Agency (EMA) committee recommending against European approval of Zelnorm® (tegaserod) for the treatment of women with irritable bowel syndrome with constipation (IBS-C).

Novartis decided to take this action after the European Committee for Medicinal Products for Human Use (CHMP) recommended that the European Commission not approve Zelnorm, which has been approved to date in 56 countries, including the US.

“Although we are disappointed with the CHMP opinion, we are confident in the clinical profile and benefits of Zelnorm. This product has been rigorously studied in more than seven placebo-controlled trials involving over 14,000 patients worldwide,” said James Shannon, Head of Global Pharma Development at Novartis Pharma AG. “The extensive clinical program and its use in patients in over 30 countries to date have clearly demonstrated the clinical benefits, efficacy and safety of Zelnorm.”

The clinical program included the ZENSAA (Zelnorm in Europe, North and South America and Africa) registration trial, which was designed in line with the recommendations from the Scientific Advice Working Group of the CHMP.

The ZENSAA results, a trial involving more than 2,600 patients, showed a statistically significant improvement in the efficacy of Zelnorm following initial as well as repeated use in women with IBS-C. Data also showed a favorable safety profile and good tolerability. Final data from this landmark study have been published in the December issue of GUT, a peer review journal published by the British Society of Gastroenterology. ZENSAA is the only IBS-C trial designed to assess the efficacy of repeated treatments and is the largest study ever conducted for this condition<sup>1</sup>.

“IBS-C can be very restricting and has a negative impact for patients, not only on a person’s health but on also their ability to work and socialize,” said Professor Jan Tack, Associate Professor and Associate Head of Clinic, Department of Gastroenterology, University of Leuven, Belgium, who also served as the lead investigator of ZENSAA. “Based on the size and scope of this trial, the results reinforce what researchers and clinicians have known for years about the clinically

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\*Novartis markets Zelnorm® (tegaserod maleate) in the US, Canada, Philippines and South Africa; and under the trademark Zelmac® (tegaserod) in Switzerland, Latin America and Asia-Pacific regions. 1/4

meaningful effect of tegaserod for the treatment of IBS-C. Now we have the added benefit with tegaserod to potentially also improve the quality of life for women with IBS-C.”

### **ZENSAA results show benefits of Zelnorm treatments**

ZENSAA results demonstrated that repeated treatment with Zelnorm was generally effective and provided relief of multiple IBS-C symptoms. Zelnorm significantly improved several aspects of quality of life as measured by validated scales. Patients in the ZENSAA trial treated with Zelnorm 6 mg twice daily experienced<sup>1</sup>:

- A significant decrease in abdominal discomfort or pain during the initial treatment and retreatment periods based on stringent efficacy criteria, which was satisfactory relief in at least three of the four weeks in the trial. Zelnorm’s treatment benefit over placebo was 9.1% ( $p < 0.001$  in initial group) and 15.9% ( $p < 0.001$  in retreatment group).
- During at least three weeks of the four-week treatment period, a total of 44.9% of Zelnorm-treated patients had significant overall IBS symptom relief compared with 28.7% on placebo in the first treatment period ( $p < 0.001$ ), which is one of the most stringent response criteria ever used in an IBS-C clinical study.
- Better quality of life scores and work productivity scores, including fewer days off work, compared with placebo ( $p = 0.05$ ).
- Improvement in overall treatment satisfaction in both treatment periods, including greater relief of IBS-C symptoms compared with previous medications and greater willingness to use Zelnorm in the future compared to placebo patients ( $p = 0.05$ ).

### **About ZENSAA**

ZENSAA was a randomized, double-blinded, placebo-controlled, multi-center trial. The first treatment period involved 2,135 patients taking 6 mg of Zelnorm twice daily and 525 patients taking placebo (4:1 ratio). Patients who responded to the initial treatment entered a treatment-free interval. Only patients whose symptoms recurring during the 12-week treatment-free interval were re-randomized. In the repeated treatment period, 488 patients were randomized to Zelnorm and 495 randomized to placebo (1:1 ratio). The trial was conducted in 262 centers in 24 countries, including the US, UK, Germany, France, Italy, Spain, Canada, Mexico and South Africa.

Data were evaluated at the end of the trial. The primary efficacy endpoints were satisfactory relief of abdominal discomfort/pain and overall IBS relief for at least three of the four weeks of treatment, also referred to as the 75% rule<sup>2</sup>. The study data were also assessed using the 50% rule, meaning satisfactory relief for at least two of the four weeks of treatment for abdominal discomfort/pain and overall IBS relief<sup>2</sup>. The study also evaluated the impact of treatment on quality of life (measured with the IBS-QOL and EQ5D scales) and treatment satisfaction as well as productivity using the WPAI-IBS tool.

ZENSAA trial results showed significant benefit with Zelnorm treatment for all endpoints when compared to placebo. Zelnorm safety and tolerability was also assessed in the trial. The adverse events profile of Zelnorm was similar to placebo, with the exception of diarrhea. Diarrhea was more frequent in patients taking Zelnorm (3.8% vs. 0.6%) in treatment Period 1. For Zelnorm-treated patients, diarrhea rarely led to discontinuation (0.9%). There was a low incidence of serious adverse events in both treatment periods (0.1% in Period 1 and 0.6% in Period 2) for Zelnorm-treated patients.

### **Irritable Bowel Syndrome with Constipation (IBS-C) and Zelnorm**

Irritable Bowel Syndrome with constipation (IBS-C) is a recurrent disorder characterized by the multiple chronic symptoms of abdominal pain and discomfort, bloating and constipation<sup>3,4,5</sup>. Serotonin (5HT), a naturally occurring chemical in the body that regulates motility and pain perception in the gut, is thought to play an important role in the normal activities of the

gastrointestinal (GI) tract. Serotonin is believed to influence the movement of food and waste through the body<sup>6,7,8</sup>. Researchers have found that an imbalance of serotonin in the gut leads to increased pain perception and dysfunction of the digestive muscles, leading to IBS symptoms<sup>9</sup>.

Zelnorm (tegaserod), a promotility agent, is the first in a newer class of medications known as serotonin-4 receptor agonists (5HT<sub>4</sub> agonists) specifically developed to treat the multiple symptoms associated with dysmotility disorders like IBS-C. By activating 5HT<sub>4</sub> receptors in the gastrointestinal tract, Zelnorm normalizes delayed motility and reduces sensitivity of the intestinal tract<sup>10,11,12</sup>. In clinical studies, significantly more patients experienced a general relief of symptoms when treated with Zelnorm, such as a decrease in abdominal pain, bloating and constipation<sup>13,14,15,16,17</sup>. In most patients, the onset of relief occurred within just one week. This medicine has been shown to be well tolerated and shows a profile of side effects similar to that of placebo with the exception of diarrhea. The majority of patients reporting diarrhea had a single episode and in most cases it occurred in the first week of treatment. The incidence of diarrhea was typically resolved with continued therapy.

Zelnorm, discovered and developed by Novartis, is approved for the treatment of IBS-C in more than 56 countries including Australia, Switzerland, Canada, the United States, Mexico, China and Brazil. Zelnorm is also approved for the treatment of Chronic Constipation in more than 20 countries including the United States, Canada and Mexico.

Novartis markets Zelnorm (tegaserod maleate) in the US, Canada, Philippines and South Africa; and under the trademark Zelmac (tegaserod) in Switzerland, Latin America and Asia-Pacific regions. For more information about IBS please visit <http://www.IBSMediacentre.com>.

The foregoing release contains forward-looking statements that can be identified by terminology such as “will appeal”, “potentially”, or similar expressions, or by express or implied discussions regarding potential additional marketing approvals or future sales of Zelnorm. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results with Zelnorm to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that the appeal described above will be successful, or that Zelnorm will receive any additional marketing approvals in any other countries, or that it will reach any particular sales levels. In particular, management's expectations regarding Zelnorm could be affected by, among other things, uncertainties relating to the appeal process; 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; increased government, industry, and general public pricing pressures; 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. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

### **About Novartis**

Novartis AG (NYSE: NVS) is a world leader in pharmaceuticals and consumer health. In 2004, the Group's businesses achieved net sales of USD 28.2 billion and pro forma net income of USD 5.6 billion. The Group invested approximately USD 4.1 billion in R&D. Headquartered in Basel, Switzerland, Novartis Group companies employ about 91,700 people and operate in over 140 countries around the world.

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

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