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Novartis provides update on regulatory status of Zelnorm® in Europe

- *CHMP issues opinion against European Union approval of Zelnorm for treatment of irritable bowel syndrome with constipation (IBS-C)*
- *Extensive clinical data involving over 14,000 patients and approvals in 56 countries, including US, demonstrate clinical benefits to patients*

Basel, March 24, 2006 – Novartis has received an opinion from the European Medicines Evaluation Agency's review committee (CHMP) recommending against approval of Zelnorm® (tegaserod) in for the treatment of women suffering from irritable bowel syndrome with constipation (IBS-C).

This advice followed an appeal procedure undertaken by Novartis in December 2005 after the Committee for Medicinal Products for Human Use (CHMP) recommended that the European Commission not approve Zelnorm.

“We are disappointed with this decision that will prevent women in Europe to have access to Zelnorm, which has proven to be clinically meaningful for the treatment of this disease,” said Dr. James Shannon, Head of Global Pharma Development at Novartis Pharma AG. “The extensive clinical trials program and its use by nearly four million patients in more than 30 countries, including the US, Canada, and Switzerland, clearly demonstrate the clinical benefits, efficacy and safety of Zelnorm.”

Zelnorm has been studied rigorously in more than seven randomized, placebo-controlled clinical trials, including more than 14,000 patients¹ from North and South America, Europe, Asia Pacific and South Africa. The Zelnorm dossier submitted to the EMEA included data from the landmark ZENSAA trial involving more than 2,600 patients. Trial results showed a statistically significant improvement in the efficacy and tolerability of Zelnorm following initial as well as repeated use in women with IBS-C.² Data also showed a favorable safety profile.²

This opinion does not have any impact on the current labeling of Zelnorm for the treatment of IBS in those countries where Zelnorm has already been approved. Zelnorm 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^A.

About ZENSAA²

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.

^A 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.

Only patients whose symptoms were 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. 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.³ 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 work productivity using the WPAI-IBS tool.

ZENSAA trial results showed significant benefit with Zelnorm treatment for all endpoints when compared to placebo. Zelnorm's safety and tolerability were 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. 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.^{4,5,6} Serotonin is believed to influence the movement of food and waste through the body.^{4,5,6} 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.^{7,8,9}

Zelnorm (tegaserod), a promotility agent, is the first in a newer class of medications known as serotonin-4 receptor agonists (5HT4 agonists) specifically developed to treat the multiple symptoms associated with dysmotility disorders like IBS-C. By activating 5HT4 receptors in the gastrointestinal tract, Zelnorm normalizes delayed motility and reduces sensitivity of the intestinal tract.^{10,11,12,13} 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. In most patients, the onset of relief occurred within just one week.^{3,14,15,16,17} 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.^{3,12,14,15} The majority of patients reporting diarrhea had a single episode, typically occurring in the first week of treatment and resolving with continued therapy.

The foregoing release contains forward-looking statements that can be identified by terminology such as "will" 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 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 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 offering medicines to protect health, treat disease and improve well-being. Our goal is to discover, develop and successfully market innovative products to treat patients, ease suffering and enhance the quality of life. Novartis is the only company with leadership positions in both patented and generic pharmaceuticals. We are strengthening our medicine-based portfolio, which is focused on strategic growth platforms in innovation-driven pharmaceuticals, high-quality and low-cost generics and leading self-medication OTC brands. In 2005, the Group's businesses achieved net sales of USD 32.2 billion and net income of USD 6.1 billion. Approximately USD 4.8 billion was invested in R&D. Headquartered in Basel, Switzerland, Novartis Group companies employ approximately 91,000 people and operate in over 140 countries around the world. For more information, please visit <http://www.novartis.com>.

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References

- 1 Shetzline MA, Cohard-Radice M, Joelsson B. Ischemic colitis, irritable bowel syndrome, and tegaserod - an alternative viewpoint. *Pharmacotherapy* 2005; 25:1684-1685.
- 2 Tack J, Müller-Lissner S, Bytzer P, Corinaldesi R, Chang L, Viegas A, Schnekenbuehl S, Dunger-Baldauf C, Rueegg P. A randomized controlled trial assessing the efficacy and safety of repeated tegaserod therapy in women with irritable bowel syndrome with constipation. *GUT* 2005; 54: 1707-1713
- 3 CPMP. Points to consider on the evaluation of medicinal products for the treatment of irritable bowel syndrome. 2003.
- 4 Gershon MD. Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther* 1999; 13:15-30.
- 5 Crowell MD. Role of serotonin in the pathophysiology of the irritable bowel syndrome. *Br J Pharmacol* 2004; 141:1285-1293.
- 6 Gershon MD. Review article: serotonin receptors and transporters - roles in normal and abnormal gastrointestinal motility. *Aliment Pharmacol Ther* 2004; 20 Suppl 7:3-14.
- 7 Camilleri M, Choi MG. Review article: irritable bowel syndrome. *Aliment Pharmacol Ther* 1997;11(1):3-15
- 8 Camilleri M. Serotonergic modulation of visceral sensation: lower gut. *Gut* 2002;51(Suppl1):i81-86
- 9 Coates MD, Mahoney CR, Linden DR, Sampson JE, Chen J, Blaszyk H et al. Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome. *Gastroenterology* 2004; 126:1657-1664.
- 10 Grider JR, Foxx-Orenstein AE, Jin J-G. 5-Hydroxytryptamine₄ receptor agonists initiate the peristaltic reflex in human, rat and guinea-pig intestine. *Gastroenterology* 1998; 115:370-380.
- 11 Müller-Lissner SA, Fumagalli I, Bardhan KD, Pace F, Pecher E, Nault B, et al. Tegaserod, a 5-HT₄ receptor partial agonist, relieves symptoms of irritable bowel syndrome in patients with abdominal pain, bloating and constipation. *Aliment Pharmacol Ther* 2001;15:1655-1666
- 12 Prather CM, Camilleri M, Zinsmeister AR, McKinzie S, Thomforde G. Tegaserod accelerates orocecal transit in patients with constipation-predominant irritable bowel syndrome. *Gastroenterology* 2000; 118:463-468.
- 13 Coffin B, Farmachidi JP, Rueegg P, Bastie A, Bouhassira D. Tegaserod, a 5-HT₄ receptor partial agonist, decreases sensitivity to rectal distension in healthy subjects. *Aliment Pharmacol Ther* 2003; 17:577-585.
- 14 Lefkowitz M, Shi Y, Schmitt C, Krumholz S, Tanghe J. The 5-HT₄ partial agonist, tegaserod, improves abdominal discomfort/pain and normalizes altered bowel function in irritable bowel syndrome (IBS). *Am J Gastroenterol* 1999; 94:266.
- 15 Novick J, Miner P, Krause R, Glebas K, Bliesath H, Ligozio G et al. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2002; 16:1877-1888.
- 16 Kellow J, Lee OY, Chang FY, Thongsawat S, Mazlam MZ, Yuen H et al. An Asia-Pacific, double blind, placebo controlled, randomised study to evaluate the efficacy, safety, and tolerability of tegaserod in patients with irritable bowel syndrome. *Gut* 2003; 52:671-676.
- 17 Nyhlin H, Bang C, Elsborg L, Silvennoinen J, Holme I, Rueegg P et al. A double-blind, placebo-controlled, randomized study to evaluate the efficacy, safety and tolerability of tegaserod in patients with irritable bowel syndrome. *Scand J Gastroenterol* 2004; 39:119-126.