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Glivec receives FDA priority review as first therapy to reduce recurrence of gastrointestinal stromal tumors after surgery

- *Clinical data showing unprecedented 89% reduction in risk of GIST relapse with use of Glivec after surgery are basis for FDA, EMEA, Swissmedic filings*
- *Historically, one in two patients experienced recurrence of GIST after surgery*
- *Regulatory submissions reflect continued commitment to bringing new therapeutic approaches to patients with rare diseases*

Basel, August 27 2008 — Novartis announced today that Glivec® (imatinib)* has been granted priority review status by the US Food and Drug Administration (FDA) as the first therapy to be reviewed for use after surgery in kit-positive gastrointestinal stromal tumors (GIST). FDA priority review status is granted to therapies that could potentially fill a currently unmet medical need and accelerates the standard review timing from ten to six months¹. Similar regulatory submissions have been filed in the European Union and Switzerland and will be filed in other countries shortly.

The Glivec submissions are based on data from a Phase III, double-blind, randomized, multicenter, international study of more than 700 GIST patients who had surgery to remove their tumors. The results showed a dramatic 89% reduction in risk of GIST returning after surgery (adjuvant setting) in patients treated with Glivec versus placebo².

In early 2007, the study met its primary efficacy endpoint, showing an advantage for Glivec in recurrence-free survival. At that time, following the recommendation of the independent study data monitoring committee to stop the trial accrual early, the study investigators made public the interim results and offered Glivec to patients receiving placebo³.

Approximately half of all patients with newly diagnosed GIST are considered candidates for surgical resection, or removal of their tumors. Of those who have the surgery, about half will suffer a recurrence⁴. If approved for this indication, Glivec will be the first treatment option available to GIST patients after surgery to reduce the risk of disease recurrence or to possibly prevent the disease from returning.

“FDA priority review status acknowledges the potential for Glivec to become the first post-surgery treatment available to GIST patients and may soon create a fundamental shift in the treatment of this disease,” said Herve Hoppenot, Executive Vice President, Chief Commercial Officer, Novartis Oncology.

Glivec is currently indicated in both the US and EU for the first-line treatment of metastatic or unresectable (inoperable) kit-positive GIST. If approved, the use of Glivec for the treatment of GIST in the adjuvant setting would add to its eight current indications, which

* Known as Gleevec® (imatinib mesylate) tablets in the US, Canada and Israel.

include Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) and five other rare diseases. Novartis also has a therapy for the treatment for carcinoid tumors and acromegaly and multiple treatments in the pipeline targeting rare diseases.

Filing data

The study on which the regulatory filing is based compared the recurrence-free survival of GIST patients taking Glivec 400 mg/day versus placebo for one year immediately following surgery. The results showed that 98% of patients receiving Glivec remained recurrence free at one year following surgery compared to approximately 82% of those receiving placebo³. This shows that as a result of adjuvant therapy with Glivec, there was an 89% reduction in risk of GIST returning².

The study, known as ACOSOG Z90001, was conducted at multiple cancer centers throughout the US and Canada, under a Cooperative Research and Development Agreement between Novartis and the National Cancer Institute (NCI). The study was led by the American College of Surgeons Oncology Group (ACOSOG).

The investigators reported that Glivec therapy was well tolerated by most patients, with side effects similar to those observed in previous clinical trials with Glivec. These include nausea, diarrhea and swelling (edema)³.

About gastrointestinal stromal tumors (GIST)

Gastrointestinal stromal tumors (GIST) belong to a group of cancers known as soft tissue sarcomas. They are the most common sarcomas and can be found most often in the stomach and small intestine. The incidence of GIST is estimated to be 4,500 – 6,000 new cases per year in the US (15–20 cases per million population)⁵, of which more than 90% are Kit-positive⁶. Kit – also known as CD117 – is a protein that, when mutated, has been identified as one of the major causes of GIST.

About Glivec

Glivec is approved in more than 90 countries, including the US, EU and Japan, for the treatment of all phases of Ph+ CML. Glivec is also approved in the EU, US and other countries for the treatment of patients with Kit (CD117)-positive gastrointestinal tumors (GIST), which cannot be surgically removed and/or have already spread to other parts of the body (metastasized). In Japan, Glivec is approved for the treatment of patients with Kit (CD117)-positive GIST. In the EU, Glivec is also approved for the treatment of adult patients with newly diagnosed Ph+ acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy and as a single agent for patients with relapsed or refractory Ph+ ALL. Glivec is also approved for the treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) who are not eligible for surgery. Glivec is also approved for the treatment of patients with myelodysplastic/myeloproliferative diseases (MDS/MPD). Glivec is also approved for hypereosinophilic syndrome and/or chronic eosinophilic leukemia (HES/CEL).

The effectiveness of Glivec is based on overall hematologic and cytogenetic response rates and progression-free survival in CML, on hematological and cytogenetic response rates in Ph+ ALL, and on objective response rates in GIST and DFSP. There are no controlled trials demonstrating increased survival.

Not all indications are available in every country.

Glivec contraindications, warnings and adverse events

The majority of patients treated with Glivec in clinical trials experienced adverse events at some time. Most events were of mild to moderate grade and treatment discontinuation was not necessary in the majority of cases.

The safety profile of Glivec was similar in all indications. The most common side effects included nausea, superficial edema, muscle cramps, skin rash, vomiting, diarrhea, abdominal pain, myalgia, arthralgia, hemorrhage, fatigue, headache, joint pain, cough, dizziness, dyspepsia and dyspnea, dermatitis, eczema, fluid retention, as well as neutropenia, thrombocytopenia and anemia. Glivec was generally well-tolerated in all of the studies that were performed, either as monotherapy or in combination with chemotherapy, with the exception of a transient liver toxicity in the form of transaminase elevation and hyperbilirubinemia observed when Glivec was combined with high dose chemotherapy.

Rare/serious adverse reactions include: sepsis, pneumonia, depression, convulsions, cardiac failure, thrombosis/embolism, ileus, pancreatitis, hepatic failure, exfoliative dermatitis, angioedema, Stevens-Johnson syndrome, renal failure, fluid retention, edema (including brain, eye, pericardium, abdomen and lung), hemorrhage (including brain, eye, kidney and gastrointestinal tract), diverticulitis, gastrointestinal perforation, tumor hemorrhage/necrosis, hip osteonecrosis/avascular necrosis.

Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated. Cardiac screening should be considered in patients with HES/CEL, and patients with MDS/MPD with high level of eosinophils (echocardiogram, serum troponin level).

Glivec is contraindicated in patients with known hypersensitivity to imatinib or any of its excipients. Women of childbearing potential should be advised to avoid becoming pregnant while taking Glivec.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by terminology such as “priority review”, “risk”, “commitment”, “potentially”, “will”, “if approved”, “possibly”, “potential”, “may”, or similar expressions, or by express or implied discussions regarding potential new indications or labelling for Glivec, regarding potential future revenues from Glivec, or regarding the long-term impact of a patient’s use of Glivec. Such forward-looking statements reflect the current views of the Company regarding future events, and involve known and unknown risks, uncertainties and other factors that may cause actual results with 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 or labelling in any market. Nor can there be any guarantee that Glivec will achieve any particular levels of revenue in the future. Neither can there be any guarantee 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, unexpected regulatory actions or delays or government regulation generally; unexpected clinical trial results, including unexpected new clinical data and unexpected additional analysis of existing clinical data; the company’s ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; government, industry and general public pricing pressures, and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated or expected. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

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

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