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Video: Gleevec Receives US Approval as First Treatment To Reduce Risk of Cancer Returning in Patients with Gastrointestinal Stromal Tumors

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- Use of Gleevec after surgery shows significant benefit for gastrointestinal stromal tumor (GIST) patients, dramatically reducing risk of relapse
- GIST, a life-threatening cancer, recurs in as many as one of two patients; recurrent tumors are often more aggressive than primary tumors
- For GIST patients who were assigned to Gleevec, more than nine out of 10 remained cancer-free based on a 14-month median follow up

EAST HANOVER, N.J., Dec. 19 /PRNewswire/ -- Novartis announced today that Gleevec® (imatinib mesylate) tablets* has been approved by the US Food and Drug Administration (FDA) for the post-surgery treatment of adult patients following complete surgical removal of Kit (CD117)-positive gastrointestinal stromal tumors (GIST).

To view the Multimedia News Release, go to: http://www.prnewswire.com/mnr/novartis/35423/

Gleevec is now the only post-surgery treatment indicated to delay the return of this highly aggressive cancer, filling a major need for GIST patients. The filing received FDA priority review status in August of this year, with regulatory reviews currently underway in other regions, including the European Union and Switzerland.

GIST is a life-threatening cancer of the gastrointestinal tract. After initial removal, GIST tumors can return in as many as one of two patients(1). Recurrent GISTs are often more aggressive than primary tumors, with relapses associated with lower survival rates(2).

"After surgery, my doctor told me there was a high likelihood that my gastrointestinal tumors would come back. I immediately searched for a possible solution and found the Gleevec clinical trial, which aimed to help patients like me," said Roslyn Fuller, a GIST patient. "This FDA approval is good news for me and other GIST patients who will now have the option to start treatment with Gleevec earlier to help prevent recurrence."

The approval for this new indication is based on data from a National Cancer Institute-sponsored Phase III study that showed a dramatic reduction in the return of GIST after surgery in patients treated for about one year with Gleevec versus placebo. Based on a 14-month median follow up, 91.6% of Gleevec patients remained cancer-free compared with 80.2% of those taking placebo(3).

* Known as Glivec® (imatinib) outside the US, Canada and Israel.

"When Gleevec was first approved for the treatment of inoperable and/or metastasized Kit-positive GIST six years ago, it revolutionized the treatment of this life-threatening cancer," said David Epstein, President and CEO, Novartis Oncology. "This latest FDA approval means patients can benefit from Gleevec earlier in the course of their disease."

Gleevec is now approved for nine indications, including the treatment of Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML), Kit (CD117)-positive gastrointestinal stromal tumors which cannot be surgically removed and/or have already spread to other parts of the body (metastasized) and five other rare diseases.

Filing data

The FDA regulatory filing for the adjuvant GIST indication was based on data from a Phase III, double-blind, randomized, multicenter, international study of more than 700 GIST patients who had undergone surgery to remove their tumors. The efficacy endpoint of the study was recurrence-free survival (RFS), defined as the time from the date of randomization to the date of recurrence or death from any cause. Participants were randomized to receive either Gleevec 400 mg/day or a matching placebo for one year(4).

With a median follow-up of 14 months, there were 30 RFS events out of 359 patients in the Gleevec arm (8.4%) compared to 70 RFS events out of 354 patients in the placebo arm (19.8%) (hazard ratio=0.398 [95% CI: 0.259, 0.610], $p < 0.0001$). This follow up is too short to evaluate survival(3).

The study, known as ACOSOG Z9001, 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. The study was led by the American College

of Surgeons Oncology Group (ACOSOG) in association with the Duke Clinical Research Institute(4).

The investigators reported that Gleevec therapy was generally well tolerated by most patients, with side effects similar to those observed in previous clinical trials with Gleevec. The most frequently reported adverse reactions were diarrhea, fatigue, nausea, edema, decreased hemoglobin, rash, vomiting and abdominal pain. No new adverse reactions were reported in the adjuvant GIST treatment setting that had not been previously reported in other patient populations including patients with unresectable and/or malignant metastatic GIST(4).

About gastrointestinal stromal tumors

Gastrointestinal stromal tumors (GIST) belong to a group of cancers known as soft tissue sarcomas. The most common sarcomas, they 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-positive(6). Kit -- also known as CD117 -- is a protein that, when mutated, has been identified as one of the major causes of GIST. Gleevec inhibits the activity of several proteins such as Kit.

About Gleevec

Gleevec tablets are now indicated for the adjuvant treatment of adult patients following complete surgical removal of Kit (CD117)-positive gastrointestinal stromal tumors (GIST). Gleevec® is also indicated for the treatment of patients with Kit (CD117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

Important safety information(3)

Fetal harm can occur when Gleevec is administered to a pregnant woman; therefore, women of childbearing potential should be advised to not become pregnant while taking Gleevec tablets and to avoid breast-feeding while taking Gleevec tablets because of the potential for serious adverse reactions in nursing infants. Sexually active female patients taking Gleevec should use adequate contraception. If the patient does become pregnant while taking Gleevec, the patient should be advised of the potential hazard to the fetus.

Severe congestive heart failure and left ventricular dysfunction have occasionally been reported. Most of the patients with reported cardiac events have had other co-morbidities and risk factors, including advanced age and previous medical history of cardiac disease. 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.

Dose adjustments may be necessary due to hepatotoxicity, other non-hematologic adverse reactions or hematologic adverse reactions. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example, every 2-3 months).

A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment. Patients with moderate renal impairment (CrCL = 20-39 mL/min) should receive a 50% decrease in the recommended starting dose and increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCL = 40-59 mL/min). For patients with moderate renal impairment doses greater than 400 mg are not recommended. Gleevec should be used with caution in patients with severe renal impairment.

In the Phase III GIST studies 13% of patients reported (NCI Grades 3/4) hemorrhage at any site. In the Phase II GIST study 5% of patients were reported to have severe gastrointestinal (GI) bleeds and/or intratumoral bleeds. GI tumor sites may have been the source of GI bleeds.

Patients should be weighed and monitored regularly for signs and symptoms of edema, which can be serious or life-threatening. There have also been reports, including fatalities, of cardiac tamponade, cerebral edema, acute respiratory failure, and GI perforation.

Bullous dermatologic reactions (eg, erythema multiforme and Stevens-Johnson syndrome) have also been reported. In some cases, the reaction recurred upon rechallenge. Several postmarketing reports describe patients able to tolerate the reintroduction of Gleevec at a lower dose with or without concomitant corticosteroids or antihistamines following resolution or improvement of the bullous reaction.

Consider potential toxicities-specifically liver, kidney, and cardiac toxicity, and immunosuppression from long-term use.

Gleevec is metabolized by the CYP3A4 isoenzyme and is an inhibitor of CYP3A4, CYP2D6 and CYP2C9. Dosage of Gleevec should increase by at least 50%, and clinical response should be carefully monitored, in patients receiving Gleevec with a potent CYP3A4 inducer such as rifampin or phenytoin. Examples of commonly used drugs that may significantly interact with Gleevec include ketoconazole, acetaminophen, warfarin, erythromycin and phenytoin. (Please see full Prescribing Information for other potential drug interactions).

For daily dosing of 800 mg and above, dosing should be accomplished using the 400 mg tablet to reduce exposure to iron.

Common side effects of Gleevec tablets

In the Phase III adjuvant GIST trial, the majority of both Gleevec and placebo-treated patients experienced at least one adverse reaction at some time. The most frequently reported adverse reactions were similar to those reported in other clinical studies in other patient

populations. No new adverse reactions were reported in the adjuvant GIST treatment setting that had not been previously reported in other patient populations, including patients with unresectable and/or malignant metastatic GIST.

The most commonly reported adverse events, Grade 3 and above, reported in post-surgery patients treated with Gleevec, were edema (periorbital, 1.2%; peripheral, 0.3%; facial, 0.3%), diarrhea (3.0%), abdominal pain (3.0%), rash (exfoliative, 2.7%; rash, 0.9%), nausea (2.4%), vomiting (2.4%), and fatigue (2.1%).

Drug was discontinued for adverse reactions in 57 of the Gleevec-treated patients (17%) and 11 of the placebo-treated patients (3%). Edema, gastrointestinal disturbances (nausea, vomiting, abdominal distension and diarrhea), fatigue, low hemoglobin and rash were the most frequently reported adverse reactions at the time of discontinuation.

The majority of patients who received Gleevec in the adjuvant GIST study experienced adverse reactions at some time. The most frequently reported adverse reactions (all Grades) were edema (periorbital, 47.2%; peripheral, 26.7%; facial, 6.8%), diarrhea (59.3%), fatigue (57.0%), nausea (53.1%), muscle spasms (16.3%) and myalgia (12.2%), abdominal pain (21.1%) and upper abdominal pain (6.2%), rash (exfoliative, 26.1% and rash 8.9%) and vomiting (25.5%)*.

The majority of patients who received Gleevec in the unresectable and/or metastatic GIST study experienced adverse reactions at some time. The most frequently reported adverse reactions (400 mg/day; 800 mg/day) (all Grades) were edema (77%; 86%), nausea (58%; 65%), muscle cramps (32%; 30%), diarrhea (56%; 58%), fatigue (69%; 75%), abdominal pain (57%; 55%), rash and related terms (56%; 70%), and vomiting (37%; 41%)*.

In previous Phase III unresectable and/or metastatic GIST trials (400 mg/day; 800 mg/day) severe (NCI Grades 3/4/5) lab abnormalities -- including neutropenia (3%; 4%), and anemia (5%; 6%) -- and severe adverse reactions (NCI Grades 3/4/5), including edema (9%; 13%), fatigue (12%; 12%), abdominal pain (14%; 12%), nausea (9%; 8%), diarrhea (8%; 9%), rash (8%; 9%), vomiting (9%; 8%) and myalgia (6%; 4%) were reported among patients receiving Gleevec.

In CML clinical studies, the majority of adult Ph+ CML patients who received Gleevec experienced adverse reactions at some time, but most were mild to moderate in severity. The most frequently reported adverse reactions (all Grades) were superficial edema (60%-74%), nausea (50%-73%), muscle cramps (28%-62%), vomiting (23%-58%), diarrhea (43%-57%), musculoskeletal pain (38%-49%), and rash and related terms (36%-47%)*+. In these studies, therapy with Gleevec was discontinued for drug-related adverse reactions in 2.4% to 5% of patients.

In CML clinical studies, severe (NCI Grades 3/4) lab abnormalities-including neutropenia (3.6%-48%), anemia (1%-42%), thrombocytopenia (<1%-33%), and hepatotoxicity (approx 5%)-and severe adverse experiences (NCI Grades 3/4), including severe fluid retention (e.g., pleural effusion, pulmonary edema, and ascites) and superficial edema (1.3%-11%), hemorrhage (1.8%-19%), and musculoskeletal pain (2%-9%) were reported among patients receiving Gleevec*. Severe fluid retention appears to be dose-related, was more common in the advanced phase studies (where the dosage was 600 mg/day), and is more common in the elderly.

Supportive care may help management of some mild-to-moderate adverse reactions so that the prescribed dose can be maintained whenever possible. However, in some cases, either a dose reduction or interruption of treatment with Gleevec may be necessary.

Gleevec tablets should be taken with food and a large glass of water to minimize GI irritation. Gleevec tablets should not be taken with grapefruit juice and other foods known to inhibit CYP3A4.

Patients should be informed to take Gleevec exactly as prescribed, not to change their dose or stop taking Gleevec unless they are told to do so by their doctor. If patients miss a dose, they should be advised to take their dose as soon as possible unless it is almost time for their next dose, in which case the missed dose should not be taken. A double dose should not be taken to make up for any missed dose.

*Numbers indicate the range of percentages in 4 studies among adult patients, with newly diagnosed Ph+ CML, patients in blast crisis, accelerated phase, and in the chronic phase after failure of interferon-alpha therapy.

+ For more detailed study information please see full Prescribing Information.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by terminology such as "risk," "can," "likelihood," "aimed to," "will," or similar expressions, or by express or implied discussions regarding potential new indications or labelling for Gleevec or regarding potential future revenues from Gleevec. You should not place undue reliance on these statements. Such forward-looking statements reflect the current views of management regarding future events, and involve known and unknown risks, uncertainties and other factors that may cause actual results with Gleevec to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that Gleevec will be approved for any additional indications or labeling in any market. Nor can there be any guarantee that Gleevec will achieve any particular levels of revenue in the future. In particular, management's expectations regarding Gleevec 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; the impact that the foregoing factors could have on the values attributed to the Novartis Group's assets and liabilities as recorded in the Group's consolidated balance sheet, 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 Pharmaceuticals Corporation

Novartis Pharmaceuticals Corporation researches, develops, manufactures and markets leading innovative prescription drugs used to treat a number of diseases and conditions, including those in the cardiovascular, metabolic, cancer, organ transplantation, central nervous system, dermatological, GI and respiratory areas. The Company's mission is to improve people's lives by pioneering novel healthcare solutions.

Located in East Hanover, New Jersey, Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG, which provides healthcare solutions that address the evolving needs of patients and societies. Focused solely on healthcare, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic pharmaceuticals, preventive vaccines, 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 97,000 full-time associates and operate in over 140 countries around the world. For more information, please visit http://www.novartis.com.

For more information

Additional information regarding Gleevec and Novartis Oncology can be found on the websites, www.gleevec.com and www.novartisoncology.us.

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List of links present in page

1. https://prod1.novartis.com/us-en/us-en/news/media-releases/video-gleevec-receives-us-approval-first-treatment-reduce-risk-cancer-returning-patients-gastrointestinal-stromal-tumors
2. http://www.prnewswire.com/mnr/novartis/35423/
3. http://www.novartis.com/
4. http://www.gleevec.com/
5. http://www.novartisoncology.us/
6. http://www.liferaftgroup.org/gist_recurrence.html
7. http://www.cancer.gov/clinicaltrials/ACOSOG-Z9001
8. http://www.cancer.org/docroot/CRI/content/CRI_2_4_1x_What_Are_the_Key_Statistics_About_Gastrointestinal_Stromal_Tumors.asp?rnav=cri
9. http://www.ahrq.gov/clinic/ta/gist/gist1.htm
10. http://www.prnewswire.com/mnr/novartis/35423/
11. http://www.gleevec.com/
12. http://www.novartis.com/
13. http://www.prnewswire.com/comp/164550.html