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Photo: New Data Show Gleevec® Halts Progression to Advanced Stages of Life-Threatening Form of Leukemia in Sixth Year of Treatment

Dec 09, 2007

- - Risk of disease progression continues to drop from the second year of treatment; no patients taking Gleevec in sixth year progressed from initial disease phase
- - Long-term survival trend may suggest many patients could approach normal life expectancy with continued treatment

EAST HANOVER, N.J., Dec. 9 /PRNewswire-FirstCall/ -- New data from the largest clinical trial in newly diagnosed patients with a life-threatening form of leukemia showed that long-term use of Gleevec® (imatinib mesylate) tablets(1) can halt progression to advanced disease stages in the sixth year of treatment.

To view the Multimedia News Release, go to: http://www.prnewswire.com/mnr/novartis/31035/

Results of the International Randomized Interferon versus STI571 (IRIS) study reveal that after two years of treatment the rate of disease progression continued to decline and fell to 0% in the study's sixth year. In addition, the estimated overall six-year survival rate for patients treated with Gleevec was 88%.

Lead investigators presented the latest findings from this landmark study involving more than 1,100 newly diagnosed patients with a form of the disease known as Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) at the 49th Annual Meeting of the American Society of Hematology (ASH).

Patients in the initial (chronic) phase of CML who received continuous treatment with Gleevec did not progress to advanced stages of the disease. Without treatment, CML typically progresses over three to five years from the initial phase through a transition (accelerated) phase to a rapidly fatal form called blast crisis(1).

"If this survival trend continues, many patients with CML may approach normal life expectancy with continued Gleevec treatment," said Brian Druker, MD, director of the Oregon Health & Science University Cancer Institute Center; the JELD-WEN Chair of Leukemia Research, Howard Hughes Medical Institute Investigator and a member of the National Academy of Sciences.

Most CML patients are in the chronic phase when the disease is diagnosed. Before Gleevec was available, about 50% of patients with Ph+ CML progressed from the initial phase to more advanced stages after only three to five years(2). Once patients reached the final blast crisis phase, survival was generally three to six months(3).

With a unique six-year record of safety and efficacy, Gleevec remains the first-line drug therapy for all patients with Ph+ CML.

Gleevec has continued to be generally well tolerated as initial drug therapy for Ph+ CML in chronic phase. At the six-year follow-up, the type and frequency of adverse events were similar to previously reported profiles.

Newly occurring or worsening grade 3 or 4 hematologic or biochemical adverse events were infrequent.

IRIS is an open-label Phase III clinical trial enrolling 1,106 newly diagnosed patients with Ph+ CML in chronic phase in 177 centers across 16 countries. There are two arms to the study: one group of patients received Gleevec 400 mg per day, while the other received a target dose of interferon (IFN) of 5 MIU/m2/day in combination with cytarabine (Ara-C) 20 mg/m2/day for 10 days each month. Because of tolerability issues, lack of response or loss of response, 65% of patients in the IFN/Ara-C arm crossed over to the Gleevec arm, whereas only 3% of patients in the Gleevec arm crossed over to the IFN/Ara-C arm(1).

Cumulative best responses to Gleevec treatment improved dramatically between the first and sixth years of treatment. Over the period, the number of Gleevec-treated patients showing complete cytogenetic response (or elimination of the abnormal Philadelphia chromosome associated with CML) rose from 70% in the first year to 87% by the sixth year of treatment.

The estimated overall survival rate for patients receiving Gleevec was 88% when considering deaths from all causes. When deaths from causes unrelated to CML or following transplantation are excluded, the estimated overall survival rate was 95%(1). Less than 5% of patients died of CML(1).

The rate of disease progression continued to decline in the sixth year of the study, with a 0.4% event rate (including loss of response) and a 0% rate of progression to advanced disease between years five and six among patients who remained on Gleevec after five years.

No new serious safety issues were identified between the fifth and sixth year of treatment(1).

In a separate study published last month in the ASH journal Blood, Gleevec produced a high six-year estimated overall survival rate (76%) in chronic- phase CML patients who had previously failed treatment with interferon. Most of these high-risk patients (57%) also achieved the best treatment outcome - a complete cytogenetic response - and many (40%) were still in cytogenetic response after six years of treatment with Gleevec(4).

About Gleevec

Gleevec® (imatinib mesylate) tablets is indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in the chronic phase. Follow-up is limited to 5 years. Gleevec is also indicated for the treatment of patients with Ph+ CML in blast crisis (BC), accelerated phase (AP), or in the chronic phase (CP) after failure of interferon-alpha therapy.

Important Safety Information

Fetal harm can occur when 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 (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 (eg, 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(2). 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.

Severe congestive heart failure and left ventricular dysfunction have occasionally been reported. Most of the patients with reported cardiac events have had other comorbidities 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 nonhematologic adverse reactions, or hematologic adverse reactions. Therapy with Gleevec was discontinued for drug-related adverse reactions in 2.4% to 5% of patients.

A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment.

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, increased intracranial pressure, papilledema, and gastrointestinal (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

The majority of adult Ph+ CML patients who received Gleevec in clinical studies 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%).(3,4)

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 does 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.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by terminology such as "may," "could," "can" or similar expressions, or by express or implied discussions regarding the long-term impact of a patient's use of Gleevec or potential future sales of Gleevec. Such forward-looking statements 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 regarding the long-term impact of a patient's use of Gleevec. Nor can there be any guarantee regarding potential future sales of Gleevec. In particular, management's expectations regarding Gleevec could be affected by, among other things, unexpected clinical trial results, including unexpected additional analysis of Gleevec clinical data, and unexpected new clinical data; 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; government, industry, and general public pricing pressures; and other risks and factors referred to in Novartis' 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 this information as of this date and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

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(1) Known as Glivec® (imatinib) outside the U.S., Canada and Israel.

(2) Numbers indicate the range of percentages in 4 studies among adult patients with Ph+ CML in blast crisis, accelerated phase, and chronic phase.

(3) Numbers indicate the range of percentages in 4 studies among adult patients with Ph+ CML in blast crisis, accelerated phase, and chronic phase.

(4) For more detailed study information please see full Prescribing

Information.

References

1. Hochhaus, A. IRIS 6-Year Follow-Up: Sustained Survival and Declining Annual Rate of Transformation in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with Imatinib. Oral Presentation. American Society of Hematology Annual Meeting, 2007. Abstract #25.
2. Faderl S; Talpaz M; Estrov Z; O'Brien S; Kurzrock R; Kantarjian HM. The biology of chronic myeloid leukemia. N Engl J Med. 341:164-72, 1999.
3. Besa, Emmanuel C. Chronic Myelogenous Leukemia. E-Medicine, WebMD. Available at: http://www.emedicine.com/med/topic371.htm. Accessed 30 November, 2007.
4. Hochhaus, A., Druker, B. et al. Favorable long-term follow-up results over six years for response, survival and safety with imatinib mesylate therapy in chronic phase chronic myeloid leukemia post failure of interferon alpha treatment. Blood, 2007.

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