AUTHORIZATION WITH CONDITIONS OF PrTASIGNA* (nilotinib) 150 mg CAPSULES FOR THE TREATMENT OF ADULT PATIENTS WITH NEWLY DIAGNOSED PHILADELPHIA CHROMOSOME POSITIVE CHRONIC MYELOID LEUKEMIA (Ph+ CML) IN CHRONIC PHASE

DEAR HEALTH CARE PROFESSIONAL LETTER

NOVARTIS

June 9, 2011

Dear Health Professional(s):

Novartis Pharmaceuticals Canada Inc. is pleased to announce that Health Canada has granted a Notice of Compliance under the Notice of Compliance with Conditions (NOC/c) Policy to TASIGNA* (nilotinib capsules) 150 mg as an oral therapy for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP).

Health Canada has issued a market authorization with conditions under the NOC/c Policy for TASIGNA* to reflect the promising evidence of the clinical effectiveness of TASIGNA* in adult patients with this life-threatening disease, and the need for further follow-up to confirm the clinical benefit.

This NOC/c is based on the interim analysis of the major molecular response (MMR) rates (the primary endpoint) at 12 months, in an ongoing open label, multi-center, Phase III study A2303 (ENESTnd). MMR was defined as $\leq$ 0.1% BCR-ABL/ABL % by international scale measured by Real-Time Quantitative PCR (RQ-PCR), which corresponds to a $\geq$ 3 log reduction of BCR-ABL transcript from standardized baseline. Study A2303 was designed to assess whether the treatment of newly diagnosed, previously untreated patients with Ph+ CML-CP treated with twice daily doses of 300 mg (n=282) and 400 mg (n=281) of nilotinib demonstrates superior efficacy compared to 400 mg imatinib (n=283) given once daily. Patients were randomized 1:1:1. Complete cytogenetic response (CCyR) by 12 months and progression to accelerated phase and blast crisis (AP/BC) on treatment were evaluated as the secondary endpoints.

Efficacy of TASIGNA* was demonstrated based on 846 patients enrolled. Baseline characteristics were well balanced between the three groups. All patients completed 12 months of treatment (or discontinued earlier). The median time on treatment is slightly over 18 months in all three treatment groups. In each treatment arm, more than 80% of patients had received treatment for longer than 12 months.

Study Results

MMR (Primary efficacy endpoint):
MMR rate at 12 months was statistically significantly superior in the nilotinib 300 mg twice daily arm compared to the imatinib 400 mg once daily arm (44.3% vs. 22.3%, $p<0.0001$). The rate of MMR at 12 months, was also statistically significantly higher in the nilotinib 400 mg twice daily arm compared to the imatinib 400 mg once daily arm (42.7% vs. 22.3%, $p<0.0001$).

CCyR (Secondary efficacy endpoint):
CCyR was defined as 0% Ph+ metaphases in the bone marrow based on a minimum of 20 metaphases evaluated. CCyR rate by 12 months (includes patients who achieved CCyR at or before the 12 month time point as responders) was statistically higher for both the nilotinib 300 mg twice daily arm compared to imatinib 400 mg once daily arm (80.1% vs. 65.0%, $p<0.0001$) and the nilotinib 400 mg twice daily arm compared to imatinib 400 mg once daily arm (77.9% vs. 65.0%, $p=0.0005$).

Progression to accelerated phase and blast crisis (AP/BC) on treatment (Secondary efficacy endpoint):
Overall by the cut-off date, 15 patients progressed to AP or BC (2 in the nilotinib 300 mg twice daily arm, 1 in the nilotinib 400 mg twice daily arm and 12 in the imatinib 400 mg once daily arm). No patients who progressed had achieved MMR. However, CCyR was achieved in 4 patients (all in the imatinib arm). The estimated rates of patients free from progression to AP or BC at 18 months were 99.3%, 99.6% and 95.4%, respectively. There was a statistically significant reduction in progression to AP or BC in the nilotinib 300 mg twice daily arm vs. imatinib arm ($p=0.0062$) and in the nilotinib 400 mg twice daily arm vs, imatinib arm ($p=0.0026$).

INDICATIONS AND CLINICAL USE

TASIGNA* (nilotinib capsules) is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.

The effectiveness of TASIGNA* is based on major molecular response and cytogenetic response rates. The study is ongoing and further data will be required to determine long-term outcome.

Patients should be advised about the nature of the market authorization with conditions for TASIGNA* in this indication.

OTHER USES OF TASIGNA*

TASIGNA* has already been issued a market authorization with conditions for the treatment of chronic phase and accelerated phase Ph+ CML in adult patients resistant to or intolerant of at least one prior therapy, including imatinib.

PHARMACOLOGY

TASIGNA* is a potent and selective inhibitor of the Abl tyrosine kinase activity of the Bcr-Abl oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukemia cells.

SERIOUS WARNINGS AND PRECAUTIONS

Based on the integrated TASIGNA* safety database of CML patients, serious warnings and precautions include:

- Sudden Cardiac Deaths
- QT interval prolongation
- Should not be used in patients with uncorrectable hypokalemia or hypomagnesemia
- Hepatotoxicity/Hepatic failure (in some cases, fatal)
- Pancreatitis
- Myelosuppression (thrombocytopenia, neutropenia and anemia)

TASIGNA* should only be prescribed by a qualified healthcare professional who is experienced in the use of antineoplastic therapy and with the treatment of CML. For further details, see the TASIGNA* Product Monograph.

ADVERSE REACTIONS

The majority of TASIGNA* treated patients experienced adverse reactions. Discontinuation for adverse events regardless of causality was observed in 7% of newly diagnosed patients with Ph+ CML-CP receiving TASIGNA* at the recommended dose (300 mg twice daily).

The following adverse drug reactions were reported in newly diagnosed patients with Ph+ CML-CP receiving TASIGNA* at the recommended dose of 300 mg twice daily:

Non-Hematologic Adverse Drug Reactions

- Very Common (≥10%): rash, pruritus, headache, nausea, fatigue, and myalgia. Most of these ADRs were mild to moderate in severity (Grade 1 or 2).
- Common (≥1% - <10%): Upper abdominal pain, alopecia, constipation, diarrhea, dry skin, muscle spasms, arthralgia, vomiting, abdominal pain, peripheral oedema and asthenia. They were mild to moderate severity, manageable and generally did not require dose reduction.

Abnormal Hematologic and Clinical Chemistry Findings

- Grades 3/4 neutropenia (12%), thrombocytopenia (10%), and anemia (4%).
- Grade 3/4 elevation in total bilirubin (4%), lipase (7%), alanine aminotransferase (ALT) (4%) and Grade 3/4 hyperglycemia (6%).

Cardiac Events

- Maximum QTcF mean increase from baseline was 10.4 msec (two-sided 90% Upper CI: 11.9).
- QTcF increase from baseline of >60 msec in 1 patient.
- No patients with an absolute QTcF >500 msec and no episodes of Torsade de Pointes were observed.
- Pleural and pericardial effusions (1%).
- Cardiac failure in 1 patient.
- No patients in any treatment groups had a LVEF <45% during treatment. Also, there were no patients with 15% or greater decrease from baseline in LVEF.

Other Events

- Gastrointestinal and CNS hemorrhage in 2% and <1% patients, respectively.
- Deep vein thrombosis in 1 patient.

Events from other clinical trials:

- Hy's Law case (1fatal hepatotoxicity).
- Tumour lysis syndrome.
- Interstitial lung disease.
- Rhabdomyolysis.
- Peripheral arterial occlusive disease (including femoral artery stenosis), coronary and carotid artery stenosis, and cerebrovascular accident.

DRUG INTERACTIONS

Drugs That May Increase TASIGNA* Concentrations

TASIGNA* is metabolized by CYP3A4 and is also a substrate for P-gP. Concomitant use of TASIGNA* with CYP3A4 and/or P-gP inhibitors or inducers should be avoided.

Drugs That May Decrease TASIGNA* Concentrations

Co-administration of a single dose of nilotinib and esomeprazole was associated with a modest decrease in nilotinib absorption. TASIGNA* may be used concurrently with esomeprazole or other proton pump inhibitors as needed.

Drugs That May Have Their Concentration Altered by TASIGNA*

TASIGNA* is a CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1 inhibitor *in vitro*. TASIGNA* is also a P-glycoprotein (P-gP) inhibitor.

Concomitant use of TASIGNA* and CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1, as well as P-gP substrates may increase the concentrations of the substrates. TASIGNA* was not found to alter the pharmacokinetics or pharmacodynamics of warfarin. TASIGNA* can be used concurrently with warfarin. Control of warfarin pharmacodynamic markers (INR or PT) following initiation of TASIGNA*therapy (at least during the first 2 weeks) is recommended.

Anti-arrhythmic Medicines and Other Drugs That May Prolong QT

Since TASIGNA* prolongs the QT interval, concomitant use with anti-arrhythmic medicines and other drugs that may prolong the QT interval should be avoided.

FOOD INTERACTIONS

TASIGNA* absorption is increased if taken with food. Products and juices containing grapefruit, star fruit, pomegranate, Seville oranges and other similar fruits that are known to inhibit CYP3A4 should be avoided at any time.

Total Gastrectomy

TASIGNA* bioavailability was shown to be reduced in patients administered 400 mg b.i.d with total gastrectomy.

DOSAGE AND ADMINISTRATION

The recommended dose of TASIGNA* is 300 mg twice daily administered orally at approximately 12 hour intervals. Treatment should continue as long as the patient continues to benefit.
TASIGNA* must NOT be taken with food. The capsules should be swallowed whole with water. No food should be consumed for at least 2 hours before the dose is taken and no additional food should be consumed for at least one hour after the dose is taken.

For further details, see the TASIGNA* Product Monograph.

CML ALLIANCE Program:

Novartis has created the CML ALLIANCE Program, which is a patient support program designed to provide patient health information and reimbursement assistance for patients who have been prescribed TASIGNA* as indicated in the Product Monograph. This specialized patient support program represents a service offered at no cost to the patient and is fully confidential. For more information please call toll free 1-877-CML-ALLI (1-877-265-2554).

Novartis Pharmaceutical Canada Inc.
385, Bouchard Blvd.,
Dorval, Quebec, H9S 1A9

Reporting Suspected Side Effects

You can report any suspected adverse reactions associated with the use of health products in the Canada Vigilance Program by one of the following 3 ways:
Report online: www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, ON K1A0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, contact your health care professional. The Canada Vigilance Program does not provide medical advice.

Should you have medical enquiries regarding TASIGNA*, kindly contact our Medical Information Department at 1-800-363-8883.

Simon J. Alexander, M.Sc.
Director, Drug Regulatory Affairs

Jean-Marie Leclerc, M.D. FRCP(C)
Chief Scientific Officer and Senior Vice-President
Clinical and Regulatory Affairs

PrTASIGNA* (nilotinib capsules) and PrGLEEVEC* (imatinib mesylate) are a registered trademarks.