AUTHORIZATION WITH CONDITIONS OF PrTASIGNA* 200 MG CAPSULES FOR THE TREATMENT OF CHRONIC Ph+ CML IN ADULT PATIENTS RESISTANT TO OR INTOLERANT OF AT LEAST ONE PRIOR THERAPY, INCLUDING IMATINIB

DEAR HEALTH CARE PROFESSIONAL LETTER

NOVARTIS

July 19, 2010

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) 200 mg capsules, an oral therapy for the **treatment of chronic phase (CP) Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in adult patients resistant to or intolerant of at least one prior therapy, including imatinib**.

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. Overall survival benefit has not been demonstrated.

This NOC/c is based on the interim analysis of an ongoing Phase II open label, multicenter study:

- 280 CML-CP patients enrolled: 69% imatinib-resistant, 31% imatinib-intolerant
- Primary efficacy endpoint: Major Cytogenetic Response (MCyR) rate (unconfirmed)
- Secondary efficacy endpoint: Complete Hematologic Response (CHR) rate (unconfirmed)
- Median duration of treatment was 261 days.
- Dose: TASIGNA* administered on a continuous basis, (400 mg twice daily 2 hours after a meal and no additional food for at least one hour) unless there was evidence of inadequate response or disease progression. Dose escalation to 600 mg b.i.d. was allowed.

Study Results

- Prior imatinib dose:
    - median highest prior imatinib dose was 600 mg/day
    - 72% of patients received ≥ 600 mg/day
    - 40% of patients received ≥ 800 mg/day

MCyR

MCyR rate is defined as elimination (complete cytogenetic response, CCyR) or significant reduction to <35% Ph+ metaphases (partial cytogenetic response, PCyR) of Ph+ hematopoietic cells.

MCyR was 52%

INDICATIONS AND CLINICAL USE

TASIGNA* (nilotinib capsules) is indicated for the treatment of chronic phase Ph+ CML in adult patients resistant to or intolerant of at least one prior therapy, including imatinib.

Overall survival benefit has not been demonstrated.

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

OTHER USES OF TASIGNA*

TASIGNA* has been issued conditional approval for the treatment of accelerated phase Ph+ CML in adult patients resistant to or intolerant of at least one prior therapy, including imatinib.

PHARMACOLOGY

TASIGNA* is a potent 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 438 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.

WARNINGS AND PRECAUTIONS

- 14 cases of sudden cardiac deaths (uncommon frequency of 0.26%)
- new onset diabetes (uncommon frequency)
- 4 cases of vasculitis (including 1 cerebral)
- 5 cases of rhabdomyolysis

ADVERSE REACTIONS

The majority of TASIGNA* treated patients experienced adverse reactions. Sixteen percent of CML-CP patients discontinued for adverse events.

Non-Hematologic Drug-Related Adverse Events

- Most frequent: rash, pruritus, nausea, headache, fatigue, constipation, and diarrhea
- Less common: Bone pain, arthralgia, muscle spasms and peripheral oedema. Most of these adverse events were mild to moderate in severity
- Grade 3/ 4 elevation in total bilirubin (9%), lipase (15%), alanine aminotransferase (ALT) in 4% and Grade 3/ 4 hyperglycemia (11%)

Abnormal Hematologic and Clinical Chemistry Findings

- Grades 3/4 neutropenia (28%), thrombocytopenia (28%), and anemia (8%)

Cardiac Events

- QTcF >500 msec in 3 patients (< 1%). QTcF change from baseline of >60 msec in 6 patients (1.9%) and >30 msec in 105 patients (33%). No episodes of Torsade de Pointes (transient or sustained) were observed
- pleural and pericardial effusions as well as complications of fluid retention (<1%)
- congestive heart failure (<1%)

Other Events

Gastrointestinal and CNS hemorrhage in <1% and <1% patients, respectively

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 nilotinib 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 with total gastrectomy

DOSAGE AND ADMINISTRATION

The recommended dose of TASIGNA* is 400 mg twice daily administered orally at approximately 12 hour intervals. Treatment should continue as long as the patient does not show evidence of progression or unacceptable toxicity.

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).

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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 0701C
  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.

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PrTASIGNA* (nilotinib capsules) is a registered trademark.