AUTHORIZATION WITH CONDITIONS OF PrGLEEVEC* (imatinib mesylate) 100 MG AND 400 MG TABLETS FOR THE ADJUVANT TREATMENT OF ADULT PATIENTS WHO ARE AT INTERMEDIATE TO HIGH RISK OF RELAPSE FOLLOWING COMPLETE RESECTION OF KIT (CD117) POSITIVE GIST

DEAR HEALTH CARE PROFESSIONAL LETTER

December 10, 2009

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 for GLEEVEC* (imatinib mesylate) 100 mg and 400 mg tablets, an oral protein-tyrosine kinase inhibitor indicated for the adjuvant treatment of adult patients who are at intermediate to high risk of relapse following complete resection of Kit (CD117) positive gastrointestinal stromal tumors (GIST).

Health Canada has issued a marketing authorization with conditions under the Notice of Compliance with Conditions policy for GLEEVEC* (imatinib mesylate) 100 mg and 400 mg tablets based on the promising nature of the clinical efficacy and safety of GLEEVEC* in adult patients with this serious disease and the need for further follow up to verify the clinical benefit.

This NOC/c is based on results of a multicentre, double-blind, placebo-controlled, randomized Phase III study (ACOSOG-Z9001) involving 713 patients. The ages of these patients ranged from 18 to 91 years. Patients who were included had a histologic diagnosis of primary GIST expressing KIT protein by immunochemistry and a tumor size ≥3 cm in maximum dimension, with complete gross resection of primary GIST within 14 to 70 days prior to registration. After complete gross resection of primary GIST, patients were randomized to one of the two arms: GLEEVEC* at 400 mg/day or matching placebo for one year. The primary efficacy endpoint of the study was recurrence free survival (RFS). RFS was defined as the time from date of randomization to the date of recurrence or death from any cause.

After one year of adjuvant treatment, GLEEVEC* substantially reduces the rate of recurrence of Kit (CD117) positive GIST compared with placebo. At a median follow up of 14.0 months, there had been 30 RFS events in the GLEEVEC* arm and 70 RFS events in the placebo arm (hazard ratio = 0.398 [95%CI: 0.259 to 0.610], two-sided log-rank $p<0.0001$). Based on an interim analysis, the trial was stopped early and placebo patients were allowed to cross over to GLEEVEC*. Overall survival data are immature due to short follow up time.

Risk of recurrence was also retrospectively assessed in this trial based on the prognostic factors of tumor size, mitotic index, and tumor location. Mitotic index data were available for 556 of 713 patients in the intent to treat (ITT) population. The results of subgroup analyses using the United States National Institutes of Health (NIH) and the Armed Forces Institute of Pathology (AFIP) risk classifications demonstrate benefit from use of adjuvant GLEEVEC* in the moderate and high risk groups, but not in the low and very low risk groups.

INDICATIONS AND CLINICAL USE

GLEEVEC* (imatinib mesylate) is indicated for the adjuvant treatment of adult patients who are at intermediate to high risk of relapse following complete resection of Kit (CD117) positive GIST.

Conditional approval in the adjuvant GIST indication was based on recurrence free survival after one year of adjuvant therapy. The optimal treatment duration with GLEEVEC* is not known. Overall survival data are not available.

Patients should be advised about the conditional nature of the market authorization for GLEEVEC* in this indication.

OTHER INDICATIONS OF GLEEVEC*

GLEEVEC* has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit for the following indications:

- The treatment of adult and pediatric patients with newly diagnosed, Philadelphia-chromosome-positive, chronic myeloid leukemia (CML) in chronic phase.

- The treatment of adult patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).

GLEEVEC* has been issued non-conditional approval for the following indications:

- The treatment of adult patients with Philadelphia chromosome-positive CML in blast crisis, accelerated phase or chronic phase (after failure of interferon-alpha therapy).

- The use as a single agent for induction phase therapy in adult patients with newly-diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL).

- The treatment of adult patients with relapsed or refractory Ph+ ALL as monotherapy.

- The treatment of adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.

- The treatment of adult patients with aggressive sub-types of systemic mastocytosis (ASM and SM-AHNMD[1]) without the D816V c-Kit mutation. If c-Kit mutational status in patients with ASM or SM-AHNMD[1] is not known or unavailable, treatment with GLEEVEC* may be considered if there is no satisfactory response to other therapies.

- The treatment of adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) with FIP1L1-PDGFRα rearrangement.

- The treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

[1] ASM: Aggressive systemic mastocytosis; SM-AHNMD: Systemic mastocytosis with an associated clonal hematological non-mast-cell disorder.

WARNINGS AND PRECAUTIONS

Based on the GLEEVEC* integrated safety database, the following is a summary of the most serious warnings and precautions. For a complete list and further details refer to the GLEEVEC* Product Monograph.

- Severe congestive heart failure (CHF) and reduction of left ventricular ejection fraction (LVEF) have been observed;
- Rhabdomyolysis has been rarely observed;
- Severe hemorrhages may occur;
- Fluid retention may occur;
- Liver failure (in some cases, fatal) may occur;
- Gastrointestinal perforation (in some cases, fatal) may occur.

PHARMACOLOGY

GLEEVEC* is a small molecule protein-tyrosine kinase inhibitor (TKI) that inhibits the activity of several tyrosine kinases (TK) that play an important role within certain cancer cells. The activity of one of these tyrosine kinases known as KIT, is implicated in tumor growth, and metastatic progression of most GISTs.

ADVERSE REACTIONS

GLEEVEC* as adjuvant therapy was well tolerated by most of the GIST patients during the Phase III trial, ACOSOG-Z9001. 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 and include 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.

DRUG INTERACTIONS

CYP3A4 inhibitors (e.g. ketoconazole, erythromycin, clarithromycin, itraconazole, grapefruit juice), when used concomitantly with GLEEVEC*, may increase the serum concentration of imatinib. CYP3A4 inducers (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, Phenobarbital or St. John's Wort), when used concomitantly with GLEEVEC*, may significantly reduce exposure to imatinib. In patients in whom rifampin or other CYP3A4 inducers are indicated, alternate therapeutic agents with less enzyme induction potential should be considered.

Certain drugs may have their plasma concentration altered by GLEEVEC*. For further information on drug interaction details refer to the GLEEVEC* Product Monograph.

DOSAGE AND ADMINISTRATION

The recommended dose of GLEEVEC* is 400 mg/day for the adjuvant treatment of adult patients at intermediate to high risk of relapse following complete resection of Kit (CD117) positive GIST. In the clinical study, GLEEVEC* was administered for one year. The optimal treatment duration with GLEEVEC* is not known.

For further details, see the GLEEVEC* Product Monograph.

GIST ALLIANCE Program:
Novartis has created the GIST ALLIANCE Program, which is a patient support program (PSP) designed to provide patient health information and reimbursement assistance to patients who have been prescribed GLEEVEC* as indicated in the Product Monograph. This specialized PSP represents a service offered at no cost to the patient and is fully confidential. For more information please call toll free 1-866-996-GIST (1-866-996-4478).

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

Maria Perrotta
Director, Drug Regulatory Affairs
Specialty Medicines

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

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.
Dorval, (QC) H9S 1A9
Phone: 1-877-631-6775 x 3425 (Drug Safety & Epidemiology)

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at 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 K1A 0K9

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 side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

*GLEEVEC is a registered trademark.