AUTHORIZATION WITH CONDITIONS FOR Pr ZYKADIA™ 150 MG CAPSULES

DEAR HEALTH CARE PROFESSIONAL LETTER

NOVARTIS

March 23, 2015

Dear Health Care Professional(s):

Novartis Pharmaceuticals Canada Inc. is pleased to announce that Health Canada has issued a Notice of Compliance with Conditions under the Notice of Compliance with Conditions (NOC/c) policy for ZYKADIA™ (ceritinib) 150 milligram (mg) capsules for use as monotherapy in patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have progressed on or who were intolerant to crizotinib.

Health Canada has issued a market authorization with conditions under the NOC/c policy for ZYKADIA™ to reflect the promising nature of the clinical data of ZYKADIA™ in patients with this serious disease, and the need for further follow-up to verify the clinical benefit. This NOC/c is based on the primary evaluation of overall response rate (ORR) and duration of response (DOR) by Investigator assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 for patients who were treated with a ZYKADIA™ dose of 750 mg in Study CLDK378X2101. An additional evaluation of ORR and DOR was also performed based on a central Blinded Independent Review Committee (BIRC) assessment according to RECIST 1.0.

ZYKADIA™ is of high quality and possesses an acceptable safety profile based on the benefit/risk assessment. As part of its condition, Novartis Pharmaceuticals Canada Inc. has undertaken to provide Health Canada with the final clinical study reports for ongoing Study CLDK378A2303: A phase III, multicenter, randomized study of oral LDK378 versus standard chemotherapy in adult patients with ALK-rearranged (ALK-positive) locally advanced or metastatic NSCLC who have been treated previously with one chemotherapy regimen (platinum doublet) and crizotinib; ongoing Study CLDK378X2101: A phase I, multicenter, open-label dose escalation study of LDK378, administered orally in adult patients with tumors characterized by genetic abnormalities in ALK; and ongoing Study CLDK378X1101: A phase I, multicenter, open-label dose escalation study of LDK378, administered orally in Japanese patients with tumors characterized by genetic alterations in ALK.

INDICATIONS AND CLINICAL USE

ZYKADIA™ (ceritinib) is indicated as monotherapy for use in patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have progressed on or who were intolerant to crizotinib.

Marketing authorization with conditions was based on a primary efficacy endpoint of overall response rate (ORR) as well as duration of response (DOR) in clinical Study CLDK378X2101, based on Investigator assessment using RECIST 1.0. There are no available data demonstrating improvement in survival or quality of life with ZYKADIA™.

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

ACTION AND CLINICAL PHARMACOLOGY

Ceritinib is a highly selective and potent ALK kinase inhibitor. Ceritinib inhibits autophosphorylation of ALK, ALK-mediated phosphorylation of downstream signaling protein-STAT3, and proliferation of ALK-dependent cancer cells both *in vitro* and *in vivo*. Ceritinib also inhibits insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (INSR), and ROS1 (ROS1, c-ros) at clinically relevant doses.

Ceritinib was demonstrated effective against EML4-ALK and NPM-ALK kinase activity in a NSCLC and lymphoma cell line, resulting in inhibition of cell proliferation *in vitro* and regression of tumors in EML-ALK and NPM-ALK derived xenografts in mouse and rat.

SERIOUS WARNINGS AND PRECAUTIONS

Based on the integrated safety database of 255 patients (246 ALK-positive NSCLC patients and 9 non-NSCLC patients) treated at the recommended dose of 750 mg of ZYKADIA™, serious warnings and precautions include:

- QT interval prolongation.
- Interstitial Lung Disease/Pneumonitis, including fatal cases.
- ZYKADIA™ has not been studied in patients with hepatic impairment or severe renal impairment requiring peritoneal dialysis or hemodialysis.
- Hepatotoxicity.
- Gastrointestinal toxicity.

ZYKADIA™ (ceritinib) should only be prescribed and supervised by a qualified physician experienced in the use of anticancer agents. For further details, see the ZYKADIA Product Monograph.

ADVERSE REACTIONS

The majority of ZYKADIA™ treated patients experienced adverse drug reactions. Diarrhea, nausea, vomiting, abdominal pain, fatigue, alanine aminotransferase (ALT) increased, decreased appetite, aspartate aminotransferase (AST) increased, constipation, neuropathy, esophageal disorder, rash and blood creatinine increased were the most common adverse drug reactions (experienced by at least 10% of the patients). For further details, see the ZYKADIA Product Monograph.

DRUG INTERACTIONS

Ceritinib is a substrate of CYP3A. Drug interactions were observed when ceritinib was co-administered with a strong CYP3A inhibitor and a strong CYP3A inducer. Based on *in vitro* data, ceritinib may inhibit CYP3A and CYP2C9 at clinically relevant concentrations. Drug interactions may occur when ceritinib is co-administered with other QTc-prolonging and heart rate-lowering drugs. For further details, please refer to the ZYKADIA Product Monograph.

DOSAGE AND ADMINISTRATION

The recommended dose of ZYKADIA™ is 750 mg taken orally once daily at the same time each day. Treatment should be continued as long as the patient is deriving clinical benefit from therapy. ZYKADIA™ capsules should be swallowed whole with water. The capsules should not be chewed or crushed. ZYKADIA™ capsules must be taken on an empty stomach. No food should be eaten for at least two hours before the dose of ZYKADIA™ is taken and for two hours after the dose of ZYKADIA™ is taken.

Access to ZYKADIA™

Novartis Pharmaceuticals Canada Inc. will introduce the ALLIANCE™ Program shortly, which is designed to provide reimbursement assistance and treatment information to patients prescribed ZYKADIA™ for the indication in the Product Monograph. This will be a service offered at no cost to the patient and will be fully confidential. For more information about the service of the ALLIANCE™ Program, please call toll free 1-855-489-4362.

For the complete prescribing information and information available for the patients/caregivers, please consult the ZYKADIA™ Product Monograph. The Product Monograph can be found at: www.novartis.ca or should you have medical enquiries regarding ZYKADIA™, contact our Medical Information Department at 1-800-363-8883.

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Reporting Suspected Side Effects
Canada Vigilance Program
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture
Address Locator: 0701C
Ottawa, Ontario
K1A 0K9
Telephone: 613-957-0337 or Fax: 613-957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Telephone: 1-866-234-2345
Fax: 1-866-678-6789
Email: CanadaVigilance@hc-sc.gc.ca

The Adverse Reaction Reporting Form and the Adverse Reaction Guidelines can be found on the Health Canada website or in The Canadian Compendium of Pharmaceuticals and Specialties.

For other inquiries related to this communication, please contact Health Canada at:
Bureau of Metabolism, Oncology and Reproductive Sciences (BMORS)
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