AUTHORIZATION WITH CONDITIONS OF TAFINLAR® (DABRAFENIB MESYLATE) IN COMBINATION WITH MEKINIST® (TRAMETINIB) FOR THE TREATMENT OF PATIENTS WITH UNRESECTABLE OR METASTATIC MELANOMA WITH A BRAF V600 MUTATION

March 6, 2015

Dear Health Care Professional;

GlaxoSmithKline Inc. is pleased to announce that Health Canada has issued a Notice of Compliance under the Notice of Compliance with Conditions (NOC/c) policy for TAFINLAR® (dabrafenib mesylate) in combination with trametinib for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Health Canada has issued a marketing authorization with conditions under the NOC/c policy for TAFINLAR® in combination with trametinib to reflect the promising nature of the clinical data of the combination in patients with this serious disease and the need for further follow-up to verify the clinical benefit. TAFINLAR® when used in combination with trametinib possesses an acceptable safety profile based on the benefit/risk.

The efficacy and safety of TAFINLAR® in combination with trametinib in the treatment of patients with BRAF V600 mutation positive unresectable or metastatic melanoma has been evaluated in a phase III double-blind, randomized, multi-centre, international clinical study (MEK115306) with 423 patients with a BRAF V600E or BRAF V600K mutation.

Treatment with the combination therapy resulted in a statistically significant improvement in investigator-assessed progression-free survival (PFS) compared with TAFINLAR® monotherapy treatment (HR 0.75; 95% CI: 0.57, 0.99; p=0.035). This represents a 25% reduction in risk of tumor progression or death in the combination therapy arm compared with TAFINLAR® monotherapy. Median PFS for the combination therapy arm was 9.3 months compared with 8.8 months for the TAFINLAR® monotherapy arm. Independent reviewer assessed PFS results were not statistically significant (HR 0.78; 95% CI: 0.59, 1.04).

The secondary endpoint of investigator assessed best confirmed overall response rate also favoured the combination therapy over TAFINLAR® monotherapy. Overall survival data were not mature at the time of the study's primary analysis.

Indications and Clinical Use

TAFINLAR® in combination with trametinib has been issued market authorization with conditions for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Patients should be advised about the conditional market authorization for this indication.

Others Uses of TAFINLAR®

TAFINLAR® as monotherapy has been issued market authorization without conditions for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Action and Clinical Pharmacology

Dabrafenib is a small molecule inhibitor of RAF kinases, including BRAF. Oncogenic mutations in BRAF lead to constitutive activation of the mitogen-activated protein kinase (MAPK) pathway (including RAS/RAF/MEK/ERK) and may promote tumour cell growth. Trametinib is a small molecule inhibitor of mitogen-activated extracellular signal regulated kinase 1 and 2 (MEK1 and MEK2). MEK1 and MEK2 are components of the MAPK pathway (including RAS/RAF/MEK/ERK). Dabrafenib and trametinib provide concomitant inhibition of the pathway at the level of the RAF and MEK kinases, respectively. The combination of dabrafenib with trametinib was synergistic in BRAF V600 mutation-positive melanoma cell lines and delayed the emergence of resistance in BRAF V600 mutation-positive melanoma xenografts.

Serious Warnings and Precautions

In addition to the Serious Warnings and Precautions observed with TAFINLAR® and trametinib monotherapies, the following are either specific to, or occur at a greater frequency when TAFINLAR® is used in combination with trametinib:

- **Non-infectious febrile events:** Pyrexia was reported in clinical trials with TAFINLAR®, and typically first occurred within two months of initiating therapy. The incidence and severity of pyrexia are increased when TAFINLAR® is used in combination with trametinib. Serious febrile drug reactions, which are defined as serious cases of fever or fever of any severity accompanied by severe rigors or chills, dehydration, hypotension or renal failure in the absence of another cause (e.g. infection), have occurred following treatment with TAFINLAR®. In the phase III study comparing TAFINLAR® in combination with trametinib to TAFINLAR® monotherapy, serious febrile drug reactions occurred in 15% (32/209) of patients who received combination therapy compared to 7% (14/211) of patients treated with the monotherapy.

- **Venous Thromboembolism:** Fatal venous thromboembolism events have occurred when TAFINLAR® was used in combination with trametinib. In a phase I/II study, deep venous thrombosis (DVT) and pulmonary embolism (PE) occurred in 6% (12/204) of patients treated with TAFINLAR® in combination with trametinib, including 2 fatalities (1%). In the phase III combination study, DVT or PE occurred in 2% (4/209) of patients receiving combination therapy and in <1% (1/211) of patients receiving TAFINLAR® monotherapy.

- **Major hemorrhagic events:** Bleeding events including major hemorrhagic events (defined as symptomatic bleeding in a critical area or organ, and fatal intracranial haemorrhages), have been reported when TAFINLAR® is used in combination with trametinib. Bleeding events (any grade) were reported in 16% (9/55) of patients treated with combination therapy in a phase I/II study, compared to 2% (1/53) treated with single agent TAFINLAR®. Major hemorrhagic events of intracranial or gastric hemorrhage occurred in 5% (3/55) and were fatal in 4% (2/55) of patients treated with the combination therapy, compared with no cases in patients treated with monotherapy. Bleeding events (any grade) were reported in 17% (35/209) of patients treated with combination therapy in the phase III study and intracranial hemorrhage was fatal in 1% (3/209) of patients.

Adverse Reactions

The safety of TAFINLAR® in combination with trametinib has been evaluated in a safety population of 209 patients with advanced or metastatic melanoma in the phase III study comparing this combination to TAFINLAR® monotherapy. Among the adverse events in the combination therapy arm, the incidences of pyrexia, chills, and diarrhea were ≥10% higher than in the monotherapy arm. Analysis of the most frequent adverse events sorted by relative risk indicates a higher risk of the following events occurring in the combination therapy arm compared with the monotherapy arm: increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), chills, pyrexia, diarrhea, peripheral edema, and hypertension.

A higher percentage of patients had adverse events leading to permanent discontinuation of study treatment in the combination therapy arm (9%) than in the monotherapy arm (5%). The percentage of patients with adverse events leading to dose interruptions and dose reductions was also higher in the combination therapy arm than with TAFINLAR® monotherapy. In the combination therapy arm, 49% and 25% of patients receiving the combination therapy had dose interruptions and reductions, respectively, compared to 33% and 13% of patients treated with the monotherapy.

Dosage and Administration

The recommended dose regimens of TAFINLAR® in combination with trametinib is 150 mg (two 75 mg capsules) given orally twice daily (corresponding to a total daily dose of 300 mg) with 2 mg of trametinib given orally once daily.

TAFINLAR® should be taken without food and with a full glass of water at least one hour before, or at least two hours after a meal, leaving an interval of approximately 12 hours between doses. TAFINLAR® should be taken at similar times every day.

When TAFINLAR® and trametinib are taken in combination, the once-daily dose of trametinib should be taken at the same time each day with either the morning dose or the evening dose of TAFINLAR®.

Treatment should continue until disease progression or the development of unacceptable toxicity.

For the complete prescribing information and information available for the patients/caregivers please consult the TAFINLAR® and MEKINIST® Product Monographs that can be found at: www.gsk.ca.

Should you have medical enquiries regarding TAFINLAR® or trametinib contact our Medical Information Department at 1-800-387-7374.

Original signed by

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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:

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