February 15, 2012

Dear Health Care Professional(s),

GlaxoSmithKline 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 ARZERRA™ (ofatumumab), 100 mg/5 mL (20mg/mL) vial and 1,000 mg/50mL (20 mg/mL) vial for intravenous infusion, for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab.

Health Canada has issued a marketing authorization with conditions under the NOC/c policy for ARZERRA™ to reflect the promising nature of the clinical data for ARZERRA™ in patients with this serious disease and the need for further follow-up to verify the clinical benefit. ARZERRA™ is of high quality and possesses an acceptable safety profile based on the benefit/risk assessment.

As part of its conditions, GlaxoSmithKline Inc. has undertaken to provide Health Canada with additional clinical data, to confirm the clinical benefit of ARZERRA™, by providing final study reports of the following clinical trials:

- Study Hx-CD20-406 entitled “A single-arm, international, multi-center trial of HuMax-CD20, a fully human monoclonal anti-CD20 antibody, in patients with B-cell chronic lymphocytic leukemia who have failed fludarabine and alemtuzumab.”
Study OMB110911 entitled “A phase III, open-label, randomized, multicenter study of ofatumumab added to chlorambucil vs. chlorambucil monotherapy in subjects with previously untreated CLL.”

Indications and Clinical Use

ARZERRA™ (ofatumumab) has been issued marketing authorization with conditions for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab. The efficacy of ARZERRA™ is based on the demonstration of durable objective responses. No data demonstrate an improvement in disease related symptoms or increased survival with ARZERRA™.

Patients should be advised about the conditional market authorization for ARZERRA™ in this indication.

Action and Clinical Pharmacology

Ofatumumab is a human monoclonal antibody (IgG1κ) that binds to a distinct epitope encompassing both the small and large extracellular loops of the CD20 molecule, a transmembrane phosphoprotein expressed on B lymphocytes from the pre-B to mature B lymphocyte stage and on B cell CLL cells. The binding of ofatumumab to the membrane-proximal epitope of the CD20 molecule induces both complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC), resulting in removal of tumour cells. Ofatumumab has also been shown to induce cell lysis in both high and low CD20 expressing cells and in rituximab-resistant cells.

Serious Warnings and Precautions

- **Infusion Reactions**: Patients should be premedicated with an intravenous corticosteroid (as appropriate), an oral analgesic, and an oral or intravenous antihistamine following the guidance in the Product Monograph. Infusion should be interrupted if infusion reactions occur.
- **Tumour Lysis Syndrome**: In patients with CLL, tumour lysis syndrome (TLS) can occur with use of ARZERRA™.
- **Cardiovascular**: Serious and/or fatal cardiovascular events have been reported following administration of ARZERRA™. Monitor patients with a history of cardiac disease closely, and discontinue ARZERRA™ in patients experiencing serious or life-threatening cardiac arrhythmias.
- **Bowel Obstruction**: Has been reported in patients receiving anti-CD20 monoclonal antibody therapy, including ARZERRA™. Patients presenting with abdominal pain, especially early in the course of ARZERRA™ therapy, should be evaluated and appropriate treatment instituted.
- **Haematology**: During treatment with ARZERRA™, obtain complete blood counts
(CBC) and platelet counts prior to therapy, at regular intervals during therapy, and more frequently if worsening anemia, neutropenia, or thrombocytopenia occurs during therapy.

- **Infections:** Serious infections can occur during and following completion of therapy with ARZERRA™. Discontinue ARZERRA™ for serious infections and institute appropriate anti-infective therapy.

- **Hepatitis B infection and reactivation:** Screen patients at high risk of hepatitis B virus (HBV) infection before initiation of therapy. Closely monitor carriers of HBV for clinical and laboratory signs of active HBV infection during, and for 6-12 months following, ARZERRA™ treatment. Discontinue ARZERRA™ in patients who develop viral hepatitis, or reactivation of viral hepatitis, and institute appropriate treatment.

- **Progressive Multifocal Leukoencephalopathy (PML):** PML has been reported in CLL patients receiving cytotoxic pharmacotherapy, including ARZERRA™. If a diagnosis of PML is suspected, ARZERRA™ should be discontinued and referral to a neurologist considered.

- **Immune:** Do not administer live viral vaccines to patients who have recently received ARZERRA™. The ability to generate immune responses to any vaccine following ARZERRA™ treatment has not been studied.

**Adverse Reactions**

The pivotal safety data for ARZERRA™ as monotherapy was derived from 223 patients with CLL, treated with the recommended dosing regimen (see below), of whom, 95 patients were refractory to fludarabine and alemtuzumab.

The most common adverse reactions (≥ 10%) were cough, pyrexia, anemia, diarrhea, neutropenia, fatigue, dyspnea, pneumonia, chills, nausea, rash, bronchitis, back pain, and upper respiratory tract infections.

**Drug Interactions**

No formal drug-drug interaction studies have been conducted with ARZERRA™.

**Dosage and Administration**

**Dosing Considerations**
ARZERRA™ is for intravenous (IV) infusion, and must be diluted prior to administration. Do not administer as an IV push or bolus.

ARZERRA™ should be administered under the supervision of a physician experienced in the use of cancer therapy and in an environment where full resuscitation facilities are immediately available.

**Premedication**
Patients should be premedicated with an intravenous corticosteroid (as appropriate), an oral
analgesic, and an oral or intravenous antihistamine prior to infusion with ARZERRA™, following the schedule in the Product Monograph

**Recommended Dose and Dosage Adjustment**

**Recommended Dosage Regimen**
The recommended dose is 300 mg ARZERRA™ for the first infusion, and 2,000 mg ARZERRA™ for all subsequent infusions. The infusion schedule is 8 consecutive weekly infusions, followed 4 weeks later by 4 consecutive monthly [that is (i.e.) every 4 weeks] infusions.

- First and second infusions: Administer over 6.5 hours through a peripheral linear indwelling catheter. The initial rate of the first and second infusion of ARZERRA™ should be 12 mL/mL. During infusion, the rate should be doubled every 30 minutes to a maximum of 200 mL/h.
- Subsequent infusions: If the second infusion has been completed without severe infusion related adverse drug reactions (ADRs), the remaining infusions (3-12) should be administered over 4 hours through a peripheral line or indwelling catheter. Initiate infusion at a rate of 25 mL/h. In the absence of infusional toxicity, the rate of infusion may be increased every 30 minutes up to a maximum of 400 mL/h.

**Dose modification and reinitiation of therapy**
Infusion related ADRs may lead to slower infusion rates. Please refer to the Product Monograph for detailed recommendations.

**Preparation and Administration**
The ARZERRA™ concentrate must be diluted in saline prior to administration, using aseptic technique. Refer to the Product Monograph for detailed instructions on the correct preparation and administration of ARZERRA™.

For the complete prescribing information and information available for the patients/caregivers, please consult the ARZERRA™ Product Monograph. The Product Monograph can be found at http://www.gsk.ca, or by requesting a copy by contacting GlaxoSmithKline Inc. at 1-800-387-7374.

Should you have medical enquiries regarding ARZERRA™, please contact our Medical Information Department at 1-800-387-7374.

Original Signed by:

Glenn Crater, M.D.
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Mississauga, Ontario
L5N 6L4

**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 0K9Te
Telephone: 613-957-0337 or Facsimile: 613-957-0335

To report an Adverse Reaction, consumers and health professionals may call toll free:
Telephone: 1-866-234-2345
Facsimile: 1-866-678-6789
E-mail: 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 Compendium of Pharmaceuticals and Specialties](#).

For other inquiries related to this communication, please contact Health Canada at:
Biologics and Genetic Therapies Directorate
E-mail: BGTD_DGO_Enquiries@hc-sc.gc.ca
Telephone: 613-946-7264
Facsimile: 613-946-5214