HEALTH CANADA APPROVES GILEAD’S ZYDELIG™ (IDELALISIB) FOR TREATMENT OF RELAPSED CHRONIC LYMPHOCYTIC LEUKEMIA AND CONDITIONALLY APPROVES ZYDELIG FOR FOLLICULAR LYMPHOMA

- First-in-Class Oral Treatment Available for Two B-Cell Blood Cancers -

Mississauga, Ontario, (April 7, 2015) – Gilead Sciences Canada, Inc. today announced that Health Canada has issued a Notice of Compliance for ZYDELIG™ (idelalisib) tablets in combination with rituximab for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL). ZYDELIG also received a Notice of Compliance with Conditions as a monotherapy for the treatment of patients with follicular lymphoma (FL) who have received at least two prior systemic regimens and are refractory to both rituximab and an alkylating agent. ZYDELIG is a first-in-class inhibitor of PI3K delta, a protein that is over-expressed in many B-cell malignancies and plays a role in the survival, proliferation and migration of these cancer cells.

CLL and FL are slow-growing incurable blood cancers, most common in adults 50 years of age and older, that can lead to life-threatening complications such as anemia, serious infection and bone marrow failure requiring treatment. As conventional chemotherapy is not curative for CLL or FL, nearly all patients will eventually relapse after their initial treatment. At relapse, patients often face fewer treatment options because they may be unable to tolerate chemotherapy, or become resistant to treatment.

“Idelalisib offers an important treatment option for Canadians living with CLL and FL at the time of relapse,” said Dr. Carolyn Owen, Assistant Professor, Division of Hematology and Hematological Malignancies, Foothills Medical Centre, Calgary. “With these cancers, relapsed patients are often unable to tolerate traditional chemotherapy and thus, they require new active treatment options, particularly if several other therapies have failed. Many of these patients have previously had limited, if any, treatment options. We are now entering a new era of management of CLL patients. In the pivotal CLL clinical study, idelalisib demonstrated a statistically significant improvement in progression-free survival.”

CLL and FL in Canada

In Canada, it is estimated that 2,065 new cases of CLL are diagnosed each year.¹ CLL represents 35 per cent of all types of leukemia in Canada.² FL is the second most common type of non-Hodgkin lymphoma (NHL), accounting for 22 per cent of all NHLs.³ FL is usually a slow-growing (indolent) type of lymphoma, and is the most commonly occurring indolent lymphoma.
“Although many people with CLL and FL continue to live active lives with medical care, patients can experience relapses in their disease, and it is at this critical time that new treatment options are desperately needed, treatments that can make a meaningful difference in the lives of people living with cancer,” said Robin Markowitz, Chief Executive Officer, Lymphoma Canada. “We know that patients, for a variety of reasons, respond differently to the same therapy – one size does not fit all. Lymphoma Canada believes that choosing the best therapy is a decision between a patient and his/her clinician. More treatment options will provide new hope for many CLL and FL patients.”

**ZYDELIG Clinical Data – Relapsed CLL and FL**

Canadian marketing authorization for ZYDELIG in relapsed CLL is supported primarily by data from a randomized, placebo-controlled Phase 3 trial (Study 116) of ZYDELIG plus rituximab (vs. rituximab + placebo) in 220 patients with relapsed CLL who were not able to tolerate standard chemotherapy. Study 116 was stopped early based on a pre-specified interim analysis performed by an external Data Monitoring Committee showing a statistically significant effect on the primary endpoint of progression-free survival. Results of Study 116 were published in *The New England Journal of Medicine* in March 2014.

Marketing authorization with conditions for ZYDELIG in FL is supported by data from a single-arm Phase 2 study (Study 101-09) of ZYDELIG monotherapy in 72 patients who have received at least two prior systemic regimens and are refractory to both rituximab and an alkylating-agent. In this study, ZYDELIG achieved an overall response rate of 54.2 per cent. Improvement in patient survival or disease-related symptoms has not been established in this indication. Results of Study 101-09 were also published in *The New England Journal of Medicine* in March 2014.

**About ZYDELIG (idelalisib)**

ZYDELIG is an oral inhibitor of phosphoinositide 3-kinase (PI3K) delta, a protein that plays a role in the activation, proliferation and viability of B cells, a critical component of the immune system. PI3K delta signaling is active in many B-cell leukemias and lymphomas, and by inhibiting the protein, this blocks several cellular signaling pathways that drive B-cell viability.

**Important Safety Information**

**Serious Warnings and Precautions**

ZYDELIG should only be prescribed by a qualified physician who is experienced in the use of anti-cancer agents.

The following list is a summary of the most serious warnings and precautions.

- **Hepatotoxicity:** Elevations of ALT and AST Grade 3 or 4 (greater than five times the upper limit of normal) have been observed in clinical trials of ZYDELIG. These laboratory findings were generally observed within the first 12 weeks of treatment, were asymptomatic, and were reversible within 3 to 4 weeks with dose interruption. While most patients resumed treatment at a lower dose, the recurrence of ALT and AST elevations was common.
• **Severe Diarrhea/Colitis:**
  Cases of severe diarrhea/colitis were reported commonly and occurred relatively late (months) after the start of a therapy with ZYDELIG. Severe diarrhea due to ZYDELIG responds poorly to antimitotility agents. Most cases resolved within a few weeks with drug interruption and additional symptomatic treatment (e.g., anti-inflammatory corticosteroid agents such as enteric budesonide), but some had a fatal outcome.

• **Pneumonitis**
  Cases of pneumonitis, some with fatal outcome, have occurred with ZYDELIG. Time to occurrence of pneumonitis after the start of therapy with ZYDELIG was highly variable, ranging from a few weeks to over one year.

For further details, see the ZYDELIG Product Monograph.

**Adverse Reactions**

**Chronic Lymphocytic Leukemia**
In the Phase 3 study in CLL, 220 previously treated patients were randomized to receive ZYDELIG (150 mg BID) + rituximab or placebo + rituximab. Serious adverse reactions were reported in 54 (49%) patients treated with ZYDELIG + rituximab. The most frequent (≥2%) serious adverse reactions reported for patients treated with ZYDELIG were pneumonia (17%), pyrexia (9%), sepsis (8%), febrile neutropenia (5%), and diarrhea (5%). Adverse reactions that led to discontinuation of ZYDELIG occurred in 11 (10%) patients. The most common adverse reactions that led to treatment discontinuations were hepatotoxicity and diarrhea/colitis. A total of 39 patients (35%) had dose interruptions, 16 patients (15%) had dose reductions, and 11 patients (10%) had drug discontinuation due to adverse reactions. Patients may have had more than one type of dose modification. The most common reasons for dose reductions were elevated transaminases, diarrhea, and neutropenia.

**Indolent Non-Hodgkin Lymphoma (iNHL)**
In the Phase 1 and 2 studies in previously treated iNHL, 146 patients were treated with ZYDELIG monotherapy at a dose of 150 mg BID. Serious adverse reactions were reported in 73 (50%) patients treated with ZYDELIG. The most frequent serious adverse reactions were pneumonia (15%), diarrhea (11%), and pyrexia (9%). Among the 146 iNHL patients who received ZYDELIG 150 mg BID as a single agent, 62 (43%) had dose interruptions, 34 (23%) had dose reductions, and 36 (25%) had drug discontinuation due to adverse reactions. Patients may have had more than one type of dose modification. The most common reasons for dose modifications were diarrhea, elevated transaminases, and neutropenia.

**Drug Interactions**
Idelalisib is metabolized primarily via aldehyde oxidase, and to a lesser extent via CYP3A and glucuronidation (UGT1A4).

A clinical drug interaction study found that coadministration of ZYDELIG with rifampin (a strong CYP3A inducer) resulted in a ~75% reduction in idelalisib plasma AUC_{inf}. Coadministration of ZYDELIG with strong CYP3A inducers such as rifampin, phenytoin, St. John’s Wort, or carbamazepine should be avoided.

A clinical drug interaction study found that coadministration of ZYDELIG with midazolam (a sensitive CYP3A substrate) resulted in a ~140% increase in C_{max} and a ~440% increase in AUC_{inf} of midazolam. Accordingly, ZYDELIG is considered to be a strong CYP3A inhibitor. Coadministration of ZYDELIG with CYP3A substrates may increase their systemic exposures.
Caution is recommended if ZYDELIG is coadministered with narrow therapeutic index CYP3A substrates (e.g., alfentanil, cyclosporine, sirolimus, tacrolimus, pimozide, fentanyl, quinidine, ergotamine, dihydroergotamine).

For further information on drug interactions, see the ZYDELIG Product Monograph.

**Dosage and Administration**

The recommended dose of ZYDELIG is 150 mg administered orally twice daily.

For information on dose modifications, see the ZYDELIG Product Monograph.

**About Gilead Sciences**

Gilead Sciences is a biopharmaceutical company that discovers, develops and commercializes innovative therapeutics in areas of unmet medical need. The company’s mission is to advance the care of patients suffering from life-threatening diseases. Gilead has operations in more than 30 countries worldwide, with headquarters in Foster City, California. Gilead Sciences Canada, Inc. is the Canadian affiliate of Gilead Sciences, Inc. and was established in Mississauga, Ontario in 2005.

**Forward-Looking Statement**

This press release includes forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 that are subject to risks, uncertainties and other factors, including the risk that physicians and patients may not see advantages of ZYDELIG over other therapies and may therefore be reluctant to prescribe the product. Further, additional studies of ZYDELIG may produce unfavorable results. These risks, uncertainties and other factors could cause actual results to differ materially from those referred to in the forward-looking statements. The reader is cautioned not to rely on these forward-looking statements. These and other risks are described in detail in Gilead’s Annual Report on Form 10-K for the quarter ended December 31, 2014, as filed with the U.S. Securities and Exchange Commission. All forward-looking statements are based on information currently available to Gilead, and Gilead assumes no obligation to update any such forward-looking statements.

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*Canadian Product Monograph for ZYDELIG is available at [www.gilead.ca](http://www.gilead.ca).*

*ZYDELIG is a trademark of Gilead Sciences, Inc. or its related companies.*

*For more information on Gilead Sciences, please visit the company’s website at [www.gilead.com](http://www.gilead.com), follow Gilead on Twitter (@GileadSciences) or call Gilead Public Affairs at 1-800-GILEAD-5 or 1-650-574-3000.*

**References:**