NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004
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This notification is a referral under Article 20 of Regulation (EC) 726/2004 to the Pharmacovigilance Risk Assessment Committee (PRAC) made by the European Commission:

Product(s) Name(s) Procedure name	Zydelig (idelalisib) Zydelig (idelalisib)
Active Substance(s)	idelalisib
Pharmaceutical form(s)	All pharmaceutical forms
Strength(s)	All strengths
Route(s) of administration	All routes of administration
Marketing Authorisation Holder(s)	Gilead Sciences International Ltd

Zydelig (idelalisib) inhibits phosphatidylinositol 3 kinase p110δ (PI3Kδ), which is hyperactive in B cell malignancies and is central to multiple signalling pathways that drive proliferation, survival, homing, and retention of malignant cells in lymphoid tissues and bone marrow. Idelalisib is a selective inhibitor of adenosine 5'-triphosphate (ATP) binding to the catalytic domain of PI3Kδ, thereby preventing activation of downstream effectors.

Zydelig (Idelalisib) is a centrally authorised product and is currently indicated in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or as first line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. Zydelig is also indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.

On 10 March 2016, the European Commission was informed of the marketing authorisation holder's intention to terminate enrolment of ongoing Phase 3 studies[i] evaluating the addition of idelalisib to standard therapies in first line CLL and relapsed indolent non-Hodgkin's lymphoma (iNHL)/small lymphocytic lymphoma (SLL). The Independent Safety Data Monitoring Committee observed increased risk of death and higher incidence of serious adverse events (SAE) early in the study among subjects receiving idelalisib compared to the control groups.

In the three trials, overall survival was decreased in the treatment arm compared to the control arms. The adverse events leading to death were mainly infections and respiratory disorders. The CLL studies evaluated combinations with chemotherapy and immunotherapy which are currently not approved. The iNHL study evaluated combination of idelalisilib and immunotherapy in a population with earlier disease characteristics than the currently approved indication for iNHL. However, in light of the current emerging safety data, there is a need to review the findings from the clinical trials and all available safety data related to idelalisib and assess their potential impact on the benefit/risk of idelalisib in the approved indications and relevant on-going variations.

In view of the above, the European Commission (EC) initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency to assess the above concerns and their impact on the benefit risk balance of Zydelig (idelalisib).

The EC requests the Agency to give its opinion as soon as possible and latest by 31 July 2016 on whether the marketing authorisation for Zydelig should be maintained, varied, suspended or revoked. The opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

In addition, the European Commission requests the Agency to give its opinion, as soon as possible, as to whether provisional measures are necessary to protect public health.

Signed [redacted] Date 11/3/2016

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Head of Medicines: policy, authorisation and monitoring

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[i] The three trials are:

- GS-US-312-0123 A Phase 3, Randomized, Double Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Bendamustine and Rituximab for Previously Untreated Chronic Lymphocytic Leukemia
- GS-US-313-0124 A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab for Previously Treated Indolent Non-Hodgkin Lymphomas
- GS-US-313-0125 A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Bendamustine and Rituximab for Previously Treated Indolent Non-Hodgkin Lymphomas