

23rd March, 2016

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Direct Healthcare Professional Communication

Restrictions on the use of Zydelig (idelalisib) for the treatment of chronic lymphocytic leukaemia (CLL) and relapsed follicular lymphoma (FL) following new clinical trial results

Dear Healthcare Professional,

In agreement with the European Medicines Agency (EMA) and the Malta Medicines Authority, Gilead wishes to inform you about important measures for the use of Zydelig (idelalisib) in the treatment of chronic lymphocytic leukaemia (CLL) and follicular lymphoma (FL) while EMA is conducting an in depth review. Interim results from three ongoing studies evaluating the addition of idelalisib to standard therapy in first line CLL and to the treatment of relapsed indolent non-Hodgkin lymphoma/small lymphocytic lymphoma (iNHL/SLL) showed increased numbers of deaths related to infections, in the idelalisib treatment arm. These clinical trials, which have now been stopped, did not evaluate the medicine in its currently authorised combinations or patient populations.

This letter sets out precautionary measures to be followed while the EMA further investigates the impact of these findings on the currently authorised use of the medicines.

Summary

Interim recommendations:

- Idelalisib should not be initiated as a first line treatment in chronic lymphocytic leukaemia (CLL) patients with 17p deletion or *TP53* mutation.
- For CLL patients with 17p deletion or *TP53* mutation already on idelalisib as first line therapy, clinicians should carefully consider individual benefit-risk balance and decide whether to continue treatment.

Indications which are unchanged:

- Idelalisib in combination with rituximab can be initiated or continued in CLL patients who have received at least one prior line of therapy.
- Idelalisib may also be initiated or continued as monotherapy in adult patients with FL refractory to two prior lines of treatment.

New risk minimisation for all patients in CLL and FL:

- Patients should be informed about the risk of serious and/or fatal infections.
- Idelalisib should not be initiated in patients with any evidence of ongoing systemic bacterial, fungal or viral infection.

- Prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) should be administered to all patients throughout idelalisib treatment.
- Patients should be monitored for respiratory signs and symptoms throughout treatment and be advised to promptly report new respiratory symptoms.
- Regular clinical and laboratory screening for cytomegalovirus (CMV) infection should be conducted. Idelalisib treatment should be discontinued in patients with evidence of infection or viraemia.
- Absolute neutrophil counts (ANC) should be monitored in all patients at least every 2 weeks for the first 6 months of treatment with idelalisib, and at least weekly in patients while ANC is less than 1,000 per mm³ (see following table).

ANC 1,000 to < 1,500/mm ³	ANC 500 to < 1,000/mm ³	ANC < 500/mm ³
Maintain Zydelig dosing.	Maintain Zydelig dosing. Monitor ANC at least weekly.	Interrupt Zydelig dosing. Monitor ANC at least weekly until ANC ≥ 500/mm ³ , then may resume Zydelig dosing at 100 mg twice daily.

Background on the safety concern

A higher incidence of serious adverse events (SAEs) and an increased risk of death occurred among patients receiving idelalisib compared to the control groups in three ongoing Phase 3 studies evaluating the addition of idelalisib to standard therapies in first line CLL and relapsed iNHL/SLL. The combined percentage of deaths in these three studies in the idelalisib arm was 7.4% compared to 3.5% in the placebo arm. The excess deaths were mainly caused by infections, including PJP and CMV infections, as well as respiratory events, some of which may have been related to infections.

The studies in iNHL/SLL included patients with disease characteristics different from those covered by the currently authorised indications or investigated a treatment combination with idelalisib not currently approved for use in iNHL patients. The clinical trial in CLL investigated idelalisib in a treatment combination that is currently not approved, however it involved patients who had not received previous treatment, some of whom had 17p deletion or *TP53* mutation.

The Zydelig Summary of Product Characteristics (SmPC) is being updated to reflect the provisional precautionary measures above. The EMA is further investigating the implication of these findings for current authorised use; any new advice will be communicated promptly.

Call for reporting

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with this product to Gilead at AM Mangion Ltd.

T: +356 23976407

E: rp@ammangion.com.mt

Alternatively reports can be submitted to the Medicines Authority;
ADR report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and
sent to postlicensing.medicinesauthority@gov.mt or sent to ADR reporting, 203 level 3, Rue
d'Argens Gzira/GZR 1368.

Company contact points

Contact Gilead Medical Information at

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Lead Responsible Person
AM Mangion Ltd.
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if you have additional questions.

Sincerely,



John McHutchison, MD

Executive Vice President, Clinical Research

Gilead Sciences, Inc.