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Zydelig®▼ (idelalisib): updated advice following conclusion of a safety review

Dear Healthcare professional,

In agreement with the European Medicines Agency (EMA) and the Health Products Regulatory Authority (HPRA), Gilead wishes to inform you of the outcome of an EU-wide review of Zydelig (idelalisib), conducted following interim results from three clinical trials which showed increased numbers of deaths related to infections in the idelalisib treatment arm and have now been stopped. These clinical trials involved patient populations and treatment combinations that are not authorised in the EU.

This letter outlines the conclusion of the review and provides an update to the advice issued in a letter sent in March.

Summary

The indication for idelalisib as first line treatment in chronic lymphocytic leukaemia (CLL) patients has now been updated as follows:

- *in combination with rituximab for the treatment of adult patients with CLL as first line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies.*

Idelalisib continues to be indicated in combination with rituximab for the treatment of adult patients with CLL who have received at least one prior therapy and as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.

Risk minimisation measures to prevent infection in all indications have been updated with further guidance regarding *Pneumocystis jirovecii* pneumonia (PJP) and cytomegalovirus (CMV) infection as follows:

- All patients should receive prophylaxis for PJP during treatment with idelalisib. This should be continued for up to 2 to 6 months after discontinuation of Zydelig. The duration of post-treatment prophylaxis should be based on clinical judgment, taking into account the patient's risk factors such as concomitant corticosteroid treatment and prolonged neutropenia.
- Regular clinical and laboratory monitoring for CMV infection is recommended in patients who are CMV-seropositive at the start of treatment with idelalisib or have other evidence of a history of CMV infection. Patients with CMV viraemia but without signs of CMV infection should also be carefully monitored. For patients with evidence of CMV viraemia and clinical signs of CMV infection, consideration should be given to interrupting idelalisib. Zydelig may be restarted if the infection has resolved and if the benefits of resuming idelalisib are judged to outweigh the risks. However, if restarted, pre-emptive CMV therapy should be considered.

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 Phase 3 clinical trials evaluating the addition of idelalisib to standard therapies in first-line CLL and early line indolent non Hodgkin lymphoma/small lymphocytic lymphoma (iNHL/SLL). The additional deaths were mainly caused by infections, including PJP and CMV infections.

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The trials 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.

Outcome following the safety review

Following completion of the EMA review, the benefit-risk balance of idelalisib in combination with rituximab for the treatment of relapsed CLL, including patients with 17p deletion or TP53 mutation, and idelalisib monotherapy for the treatment of refractory FL remains positive.

At the start of the review, based on the very limited data available EMA recommended as a precaution, that idelalisib treatment should not be initiated as a first-line treatment in CLL patients with 17p deletion or *TP53* mutation while EMA further investigated the issue. Following completion of the review, EMA has concluded that the new study results appear not to be relevant to the authorised use of Zydelig in these CLL patient subgroups, and therefore EMA recommends that Zydelig can now again be initiated in these patients. However, because efficacy and safety data are limited in treatment-naïve CLL patients with 17p deletion or *TP53* mutation, first-line treatment with idelalisib in combination with rituximab may be considered for these patients only if they are not eligible for any other therapies. Nevertheless, EMA concluded that the risk of serious infection is relevant to all indications and therefore the measures outlined in this letter to minimise this risk should be implemented.

The Zydelig Summary of Product Characteristics (SmPC) was updated in March 2016 to reflect provisional precautionary measures. Following the conclusion of the safety review by EMA, the SmPC is being further updated to amend the indication for first line treatment of CLL patients with 17p deletion or *TP53* mutation. Additional safety information about serious infections, including PJP, will be included. The following previously issued guidance is unchanged:

- Patients should be informed about the risk of serious and/or fatal infections during treatment with idelalisib.
- Idelalisib should not be initiated in patients with any evidence of ongoing systemic bacterial, fungal or viral infection.
- Patients should be monitored for respiratory signs and symptoms throughout treatment with idelalisib and be advised to promptly report new respiratory symptoms.
- 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 mm^3. Treatment should be discontinued if ANC falls below 500 per mm^3. When ANC rises above 500 per mm^3 again treatment can be restarted at a lower dose (100 mg twice daily).

Call for reporting

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with this product in accordance with the national spontaneous reporting system.

For Ireland, suspected adverse reactions should be reported to the HPRA Pharmacovigilance using a Yellow Card obtained either from the HPRA, or electronically via the website at www.hpra.ie. Adverse reactions can also be reported to the HPRA by calling +353 1 6764971.

Any suspected adverse reactions to Zydelig should be reported to Gilead Sciences Ltd. via email to Safety_FC@gilead.com or by telephone +44 (0) 1223 897500.

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Company contact point

If you have further questions or require additional information regarding the Gilead Sciences product Zydelig (idelalisib) please contact Gilead Medical Information by email at ukmedinfo@gilead.com or by telephone on +353 214 825 999.

Annexes

More information about the EMA review of Zydelig can be found here:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Zydelig/human_referral_prac_000055.jsp&mid=WC0b01ac05805c516f

Sincerely,

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