18 March 2016
EMA/201814/2016

EMA recommends new safety measures for Zydelig

Measures include close monitoring and use of antibiotics to prevent pneumonia

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) is issuing provisional advice for doctors and patients using the cancer medicine Zydelig (idelalisib) to ensure that it continues to be used as safely as possible. Zydelig is currently authorised in the EU to treat two types of blood cancers called chronic lymphocytic leukaemia (CLL) and follicular lymphoma (one of a group of cancers called non-Hodgkin lymphoma).

The PRAC recommends that all patients treated with Zydelig should receive antibiotics to prevent a particular type of lung infection (*Pneumocystis jirovecii* pneumonia). Patients should also be monitored for infection and have regular blood tests for white cell counts because low counts can increase their risk of infection. Zydelig should not be started in patients with a generalised infection. It should also not be started in previously untreated patients with CLL whose cancer cells have certain genetic mutations (17p deletion or *TP53* mutation).

These are provisional recommendations which the PRAC has issued, as a precaution, to protect patients while the medicine is being reviewed.

The review started after a higher rate of serious adverse events was seen in three clinical trials among patients receiving Zydelig compared with placebo (a dummy treatment).[1] The adverse events included deaths related to infections such as pneumonia. The clinical trials, which have now been stopped, involved patients with CLL and indolent non-Hodgkin lymphoma. However, these studies did not use the medicine in the same way as currently authorised.

Healthcare professionals will be informed in writing about the precautionary measures to be taken. Once the review is concluded, EMA will communicate further and provide guidance to patients and healthcare professionals.

Information for patients

There have been reports of serious side effects in clinical studies with the cancer medicine Zydelig. To ensure that the medicine is used as safely as possible changes have been made to the way the medicine is used:

[1] For more information see here.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

- If you are taking Zydelig, you will receive antibiotics to prevent a particular type of lung infection (*Pneumocystis jirovecii* pneumonia) and be monitored for signs of infections. You should contact your doctor straight away if you develop fever, cough or difficulty breathing.
- Your doctor will order regular blood tests to minimise the risk of infections or neutropenia (low white blood cell count which may make you more likely to develop an infection). In case of neutropenia your doctor may stop your treatment with Zydelig.
- No new patients with chronic lymphocytic leukaemia (CLL) will be started on Zydelig if they have not received previous treatment for their cancer. Patients who are already on treatment will have their treatment reviewed by their doctor.
- You should not stop Zydelig before speaking to your doctor. If you are taking Zydelig and have any questions or concerns speak to your doctor or pharmacist.
- Further information on Zydelig will be provided as necessary.

Information for healthcare professionals

- Increased rates of serious adverse effects including deaths were seen in 3 clinical trials in the treatment arm evaluating the addition of Zydelig to standard therapy in first-line CLL and relapsed indolent non-Hodgkin lymphoma. Most deaths related to infections such as *Pneumocystis jirovecii* pneumonia and cytomegalovirus infections. Other excess deaths related mainly to respiratory events.
- Studies in non-Hodgkin lymphoma included patients with disease characteristics different from those covered by the currently approved indication and investigated a combination of medicines not currently approved. The clinical trial in CLL involved patients who had not received previous treatment, some of whom had the 17p deletion or *TP53* mutation; however, it also investigated a combination of medicines which is currently not approved.
- As a precaution and while a thorough review is ongoing, Zydelig should not be started as first-line treatment in patients with CLL who have the 17p deletion or *TP53* mutation. Doctors should re-evaluate each patient taking Zydelig first-line for CLL, and only continue treatment if the benefits outweigh the risks.
- Zydelig can continue to be used in combination, only with rituximab, in CLL patients who have received at least one prior therapy, and as monotherapy in patients with follicular lymphoma that is refractory to two lines of treatment.
- Patients should be informed about the risk of serious infections with Zydelig. Zydelig must not be started in patients with any evidence of ongoing systemic infection.
- All patients should receive prophylaxis for *P. jirovecii* pneumonia during Zydelig treatment and should be monitored for respiratory signs and symptoms. Regular clinical and laboratory monitoring for cytomegalovirus infection is also recommended.
- Patients should also have regular checks of their blood counts to detect neutropenia. In case the patient has moderate or severe neutropenia treatment with Zydelig may have to be interrupted, in line with the updated summary of product characteristics (SmPC).
- Further details on these provisional measures will be provided in writing to healthcare professionals and the product information will be updated accordingly.

- Further information on the review of Zydelig will be provided as necessary and once the review is concluded.

More about the medicine

In the EU, Zydelig is authorised for the treatment of:

- chronic lymphocytic leukaemia in patients who have received previous treatment as well as in previously untreated patients who have certain genetic mutations (17p deletion or *TP53* mutation) in their cancer cells. It is only used in combination with rituximab.
- a type of non-Hodgkin lymphoma called follicular lymphoma where it is used on its own.

More information on the approved uses of Zydelig can be found here.

More about the procedure

The review of Zydelig has been initiated at the request of the European Commission, under Article 20 of Regulation (EC) No 726/2004.

The review is being carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines. While the review is ongoing the PRAC has made a set of provisional recommendations to protect public health. These will now be forwarded to the European Commission (EC), which will issue a provisional legally binding decision applicable in all EU Members States.

Once the PRAC review is concluded any further recommendations will be forwarded to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which will adopt a final opinion.

The final stage of the review procedure is the adoption by the European Commission of a legally binding decision applicable in all EU Member States.

Contact our press officer

Monika Benstetter

Tel. +44 (0)20 3660 8427

E-mail: press@ema.europa.eu