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CHMP confirms recommendations for use of Zydelig

Patients should be monitored for infection and given antibiotics during and after treatment

On 21 July 2016 CHMP (EMA's Committee for Medicinal Products for Human Use) confirmed that the benefits of Zydelig (idelalisib) in the treatment of the blood cancers chronic lymphocytic leukaemia (CLL) and follicular lymphoma outweigh the risk of side effects. However, following a review it updated recommendations to minimise the risk of serious infections in patients treated with the medicine.

All patients treated with Zydelig should be given preventive medication against the lung infection *Pneumocystis jirovecii* pneumonia during treatment and this should be continued for up to 6 months after treatment with Zydelig has stopped. Patients receiving Zydelig should also be monitored for signs of infection and have regular blood tests to measure the level of white blood cells. Low white cell counts can indicate an increased risk of infection and treatment may need to be interrupted. Zydelig should also not be started in patients with any generalised infection.

In addition, following an interim precautionary recommendation not to start Zydelig treatment in previously untreated patients with CLL that has certain genetic mutations[1], the CHMP concluded that treatment with Zydelig can again be started in these patients provided alternative treatments are not suitable and provided that the measures to prevent infection are followed.

The review, which was carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC), was started because of deaths seen in 3 studies in which Zydelig was given to patient groups for whom it is not licensed, or in unlicensed combinations with other medicines. In its review the PRAC evaluated data from these studies, together with other available evidence as well as advice from experts in this field. Although the studies did not use the medicine in the same way as currently authorised, the review concluded that the risk of serious infection had some relevance to the authorised use. The CHMP confirmed the recommendations from the PRAC review, and its opinion was sent to the European Commission which issued a final legally binding decision.

Information for patients

- There have been reports of serious infections in clinical studies with the cancer medicine Zydelig. Some changes have now been made in how the medicine is used to ensure it is given as safely as possible.

[1] 17p deletion or *TP53* mutation, see http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/03/news_detail_002490.jsp

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- If you are taking Zydelig, you will receive antibiotics to prevent a type of lung infection (*Pneumocystis jirovecii* pneumonia). Because some infections have occurred after patients had finished their cancer treatment, you will have to keep taking these antibiotics for 2 to 6 months after stopping Zydelig.
- Your doctor will regularly check you for signs of infections. If you develop fever, cough or difficulty breathing you should contact your doctor straight away.
- You will have regular blood tests to check if you have a low white blood cell count, as a low count can put you at more risk of developing an infection. Your doctor may stop your treatment with Zydelig if your white blood cell count is too low.
- You should not stop Zydelig without speaking to your doctor. If you are taking Zydelig and have any questions or concerns speak to your doctor, nurse or pharmacist.

Information for healthcare professionals

- Increased rates of serious adverse effects including deaths were seen in the treatment arm of 3 clinical trials[2] evaluating the addition of Zydelig to standard therapy in first-line treatment of CLL and relapsed indolent non-Hodgkin lymphoma. The percentage of deaths in the treatment arms was 8% in the CLL study and 8% and 5% in the lymphoma studies, compared with 3%, 6% and 1% respectively in the placebo arms. The additional deaths were mainly caused by infections, including *Pneumocystis jirovecii* pneumonia and cytomegalovirus infections.
- These studies included patients with disease characteristics that were different from those covered by the currently approved indications for Zydelig and investigated use with treatment combinations that are not currently licensed and which may have influenced the infection rate. The relevance of these results to the authorised use of Zydelig is therefore limited, but suggests a need to strengthen measures to minimise the risk of infection.
- Provided that strengthened measures are followed to minimise the risk of infection (see below), Zydelig can continue to be used in combination 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.
- Zydelig may also be used in combination with rituximab, as first line treatment in CLL in the presence of 17p deletion or *TP53* mutation provided patients cannot take any alternative treatment and provided again that the below measures are followed to reduce the risk of infection.
- 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 for 2 to 6 months after stopping treatment. Patients should be monitored for respiratory signs and symptoms. Regular clinical and laboratory monitoring for cytomegalovirus infection is also recommended and specific guidance is included in the updated summary of product characteristics (SmPC).

[2] GS-US-312-0123 a phase 3, randomised, double blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with bendamustine and rituximab for previously untreated CLL;
GS-US-313-0124 a phase 3, randomised, double blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with rituximab for previously treated iNHL;
GS-US-313-0125 a phase 3, randomised, double blind, placebo-controlled study evaluating the efficacy and safety of idelalisib in combination with bendamustine and rituximab for previously treated iNHL;

- Patients should also have regular checks of their blood counts to detect neutropenia. If the patient develops severe neutropenia, treatment with Zydelig may have to be interrupted, in line with the updated SmPC.

A letter will be sent to healthcare professionals, advising them of these changes.

More about the medicine

Zydelig is a cancer medicine containing the active substance idelalisib. In the EU, Zydelig is authorised for the treatment of two cancers of white blood cells, chronic lymphocytic leukaemia and follicular lymphoma (one of a group of cancers called non-Hodgkin's lymphomas).

- In chronic lymphocytic leukaemia, Zydelig is used in combination with another medicine (rituximab) in patients who have received at least one previous treatment and in previously untreated patients who have genetic mutations in their cancer cells called 17p deletion or *TP53* mutation and who are not eligible for other therapies.
- In follicular lymphoma, Zydelig is used on its own in patients whose disease has not responded to two previous treatments.

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

More about the procedure

The review of Zydelig was initiated at the request of the European Commission on 17 March 2016, under Article 20 of Regulation (EC) No 726/2004.

The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's opinion on 21 July 2016. The CHMP opinion was forwarded to the European Commission, which issued a final legally binding decision applicable in all EU Member States on 15 September 2016.

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